Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

How to Cite the Adult and Adolescent Opportunistic Infection Guidelines:

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed (insert date) [include page numbers, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* website (http://aidsinfo.nih.gov).

Access AIDS*info* mobile site

What's New in the Guidelines

Updates to the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents document was published in an electronic format that could be easily updated as relevant changes in prevention and treatment recommendations occur.

The editors and subject matter experts are committed to timely changes in this document because so many health care providers, patients, and policy experts rely on this source for vital clinical information.

All changes are developed by the subject matter groups listed in the document (changes in group composition are also promptly posted). These changes are reviewed by the editors and by relevant outside reviewers before the document is altered. Major revisions within the last 6 months are as follows:

May 18, 2017

1. **Tuberculosis:** In this revision, the epidemiology, diagnosis, and treatment sections for latent TB infection and TB disease were updated to include more recent statistics, diagnostic tests (e.g., IGRAs, Xpert MTB/RIF assay, LAM) and data regarding treatment (e.g., 3HP, when to start ART, new drugs for treatment of drug-resistant TB). In addition, Table 1, Table 2 and Table 3 were updated to include preferred and alternative treatment regimens, and drug-drug interactions with commonly used medications.

March 28, 2017

1. **Malaria:** The epidemiology and treatment sections were updated to include more recent statistics and data regarding treatment. Recently, Table 5 was updated to add potential drug interactions between anti-malarial medications and commonly used medications, including hepatitis C direct acting agents, antibiotics, and antifungals.

March 13, 2017

1. **Table 5** has been updated with the following key modifications:
   a. Antiretroviral drugs are removed from this table; clinicians should refer to the Adult and Adolescent Antiretroviral Treatment Guidelines' Drug Interaction section to review potential interactions and recommendations for when OI drugs are used concomitantly with certain antiretroviral drugs.
   b. Drugs used for the treatment of hepatitis C virus infection and malaria are added to this table.
2. **Table 6** has been updated with the inclusion of adverse effects associated with drugs for the treatment of hepatitis C virus infection and malaria.

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Introduction (Last updated June 17, 2013; last reviewed May 7, 2013)

Prior to the widespread use of potent combination antiretroviral therapy (ART), opportunistic infections (OIs), which have been defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons,[1,2] were the principal cause of morbidity and mortality in this population. In the early 1990s, the use of chemoprophylaxis, immunization, and better strategies for managing acute OIs contributed to improved quality of life and improved survival.[3] Subsequently, the widespread use of potent ART has had the most profound influence on reducing OI-related mortality in HIV-infected persons.[3-10]

Despite the availability of ART, OIs continue to cause considerable morbidity and mortality in the United States for three main reasons:

1. Approximately 20% of HIV-infected persons in the United States are unaware of their HIV infection,[11,12] and many present with an OI as the initial indicator of their disease;[13]
2. Some individuals are aware of their HIV infection, but do not take ART due to psychosocial or economic factors; and
3. Some patients are enrolled in HIV care and prescribed ART, but do not attain an adequate virologic and immunologic response due to inconsistent retention in care, poor adherence, unfavorable pharmacokinetics, or unexplained biologic factors.[6,14,15]

Recent analyses suggest that while 77% of HIV-infected persons who are retained in care and prescribed ART are virologically suppressed, only 20% to 28% of the total estimated HIV-infected population in the United States are virologically suppressed,[11,16] with as few as 10% in some jurisdictions.[17] Thus, while hospitalizations and deaths have decreased dramatically due to ART, OIs continue to cause substantial morbidity and mortality in HIV-infected persons.[18-28] Clinicians must be knowledgeable about optimal strategies for diagnosis, prevention, and treatment of OIs to provide comprehensive, high quality care for these patients.

It is important to recognize that the relationship between OIs and HIV infection is bi-directional. HIV causes the immunosuppression that allows opportunistic pathogens to cause disease in HIV-infected persons. OIs, as well as other co-infections that may be common in HIV-infected persons, such as sexually transmitted infections (STIs), can adversely affect the natural history of HIV infection by causing reversible increases in circulating viral load[29-34] that could accelerate HIV progression and increase transmission of HIV.[35] Thus, while chemoprophylaxis and vaccination directly prevent pathogen-specific morbidity and mortality, they may also contribute to reduced rate of progression of HIV disease. For instance, randomized trials have shown that chemoprophylaxis with trimethoprim-sulfamethoxazole can both decrease OI-related morbidity and improve survival. The survival benefit is likely to result, in part, from reduced progression of HIV infection.[36-40] In turn, the reduced progression of HIV infection would reduce the risk of subsequent OIs.

History of These Guidelines

In 1989, the Guidelines for Prophylaxis against *Pneumocystis carinii* Pneumonia for Persons Infected with the Human Immunodeficiency Virus became the first HIV-related treatment guideline published by the U.S. Public Health Service.[41] This publication was followed by a guideline on prevention of *Mycobacterium avium* complex disease in 1993.[42] In 1995 these guidelines were expanded to include the prevention of all HIV-related OIs and the Infectious Diseases Society of America (IDSA) joined as a co-sponsor.[43] These prevention guidelines were revised in 1997, 1999, and 2002 and were published in *Morbidity and Mortality Weekly Report (MMWR)*,[44-46] *Clinical Infectious Diseases*,[47-49] *The Annals of Internal Medicine*,[50,51] *American Family Physician*,[52,53] and *Pediatrics*;[54] accompanying editorials appeared in the *Journal of the American Medical Association (JAMA)*[2,55] and in *Topics in HIV Medicine*.[56]

In 2004 the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the IDSA published a new guideline including recommendations for treating OIs among HIV-infected adults and adolescents.[57] Companion guidelines were published for HIV-infected children.[58] Revised guidelines for both prevention and treatment of OIs in HIV-infected adults and adolescents[59] and HIV-exposed/infected children[60] were published in 2009.

Responses to these guidelines (e.g., numbers of requests for reprints, website contacts) demonstrate that these documents are valuable references for HIV health care providers. The inclusion of ratings that indicate both the strength of each recommendation and the quality of supporting evidence allows readers to assess the relative importance of each recommendation. The present revision includes recommendations for prevention and treatment of OIs in HIV-infected adults and adolescents; a revision of recommendations for HIV-exposed and infected children can also be found in http://www.aidsinfo.nih.gov.

These guidelines are intended for clinicians, other health care providers, HIV-infected patients, and policy makers in the United States; guidelines pertinent to other regions of the world, especially resource-limited countries, may differ with respect to the spectrum of OIs of interest and diagnostic and therapeutic capacities.

Guidelines Development Process

These guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research Advisory Council (OARAC) of the NIH. Briefly, six co-editors selected and appointed by their respective agencies (i.e., NIH, CDC, IDSA) convened working groups of clinicians and scientists with subject matter expertise in specific OIs. The co-editors appointed a leader for each working group, which reviewed the literature since the last publication of these guidelines, conferred over a period of several months, and produced draft revised recommendations. Issues requiring specific attention were reviewed and discussed by the co-editors and the leaders from each working group at the annual meeting of the IDSA in Vancouver, Canada, in October 2010. After further revision, the guidelines were reviewed by patient care advocates and by primary care providers with extensive experience in the management of HIV infection. The final document reflects further revision by the co-editors, the Office of AIDS Research (OAR), experts at CDC, and by the IDSA and affiliated HIV Medicine Association prior to final approval and publication on the AIDS*info* website. The names and affiliations of all contributors as well as their financial disclosures are provided in the Panel roster and Financial Disclosure section (Appendix C). The names of the patient advocates and primary HIV care providers who reviewed the document are listed in Contributors (Appendix D).

Guidelines Development Process (page 1 of 2)

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal prevention and management of HIV-related opportunistic infections (OIs) for adults and adolescents in the United States.
Panel members	The panel is composed of six co-editors who represent the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Disease Society of America (HIVMA/IDSA), plus more than 100 members who have expertise in HIV clinical care, infectious disease management, and research. Co-editors are appointed by their respective agencies or organizations. Panel members are selected from government, academia, and the healthcare community by the co-editors and assigned to a working group for one or more the guideline's sections based on the member's area of subject mater expertise. Each working group is chaired by a single panel member selected by the co-chairs. Members serve on the panel for a 4-year term, with an option to be reappointed for additional terms. The panel co-editors also select members from the community of persons affected by HIV disease (i.e., adults living with HIV infection, advocates for persons living with HIV infection) to review the entire guidelines document. The lists of the current panel members and of the patient advocates and primary HIV care providers who reviewed the document can be found in Appendices C and D, respectively.
Financial disclosure and management of conflicts of interest	All members of the panel submit a written financial disclosure annually reporting any associations with manufacturers of drugs, vaccines, medical devices, or diagnostics used to manage HIV-related OIs. A list of these disclosures and their last update is available in Appendix C. The panel co-editors review each reported association for potential conflict of interest and determine the appropriate action: disqualification from the panel, disqualification/recusal from topic review and discussion; no disqualification needed. A conflict of interest is defined as any direct financial interest related to a product addressed in the section of the guideline to which a panel member contributes content. Financial interests include direct receipt by the panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. Financial interest also includes direct compensation for membership on an advisory board, data safety monitoring board, or speakers' bureau. Compensation and support that filters through a panel member's university or institution (e.g., grants, research funding) is not considered a conflict of interest.
Users of the guidelines	HIV treatment providers
Developer	Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC).
Funding source	The Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in the guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or information prepared by the U.S. Food and Drug Administration or manufacturers (e.g., warnings to the public) may be used as evidence to revise the guidelines. Panel members of each working group are responsible for conducting a systematic comprehensive review of the literature, for conducting updates of that review, and for bringing to their working group's attention all relevant literature.
Method of synthesizing data and formulating recommendations	Each section of the guidelines is assigned to a working group of panel members with expertise in the area of interest. The members of the working group synthesize the available data. Recommendations are reviewed and updated by each working group after an assessment of the quality and impact of the existing and any new data. Aspects of evidence that are considered include but are not necessarily limited to the type of study (e.g., case series, prospective cohort, randomized controlled trial), the quality and appropriateness of the methods, and the number of subjects and effect sizes observed. Each revision of the guidelines is reviewed by patient care advocates and by primary care providers with extensive experience in the management of HIV infection to assess cultural sensitivity and operational utility. Finally, all material is reviewed by the co-editors, OAR, subject matter experts at CDC and the HIVMA/IDSA prior to final approval and publication.
Recommendation rating	Recommendations are rated using a revised version of the previous rating system (see How to Use the Information in this Report and Rating System for Prevention and Treatment Recommendations, below) and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. All proposals are discussed at teleconferences and by email and then assessed by the panel's co-editors and reviewed by OAR, CDC, and the HIVMA/IDSA before being endorsed as official recommendations.

Guidelines Development Process (page 2 of 2)

Topic	Comment
Other guidelines	These guidelines focus on prevention and treatment of HIV-related OIs for adults and adolescents. A separate guideline outlines similar recommendations for HIV-infected and exposed children. These guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Update plan	Each work group and the co-editors meet at least every 6 months by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by approvals of new drugs, vaccines, medical devices or diagnostics, by new information regarding indications or dosing, by new safety or efficacy data, or by other information that may affect prevention and treatment of HIV-related OIs. Updates that may significantly affect patient safety or treatment and that warrant rapid notification may be posted temporarily on the AIDS*info* website (http://www.aidsinfo.nih.gov) until appropriate changes can be made in the guidelines document.
Public comments	After release of an update on the AIDS*info* website, the public is given a 2-week period to submit comments to the panel. These comments are reviewed, and a determination is made by the appropriate work group and the co-editors as to whether revisions are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Major Changes in Guidelines Since Last Publication

Major changes in the document include:

1) New information on when to start ART in the setting of an acute OI, including tuberculosis;
2) When to start therapy for hepatitis B and hepatitis C disease, and what drugs to use;
3) Drug interactions between drugs used to manage OIs and HIV;
4) A change in the system for rating the strength of each recommendation, and the quality of evidence supporting that recommendation (see Rating System for Prevention and Treatment Recommendations); and
5) Inclusion of pathogen-specific tables of recommended prevention and treatment options at the end of each OI section, in addition to summary tables at the end of the document.

How to Use the Information in this Report

Recommendations in this report address:

1) Preventing exposure to opportunistic pathogens;
2) Preventing disease;
3) Discontinuing primary prophylaxis after immune reconstitution;
4) Treating disease;
5) When to start ART in the setting of an acute OI;
6) Monitoring for adverse effects (including immune reconstitution inflammatory syndrome [IRIS]);
7) Managing treatment failure;
8) Preventing disease recurrence ("secondary prophylaxis" or chronic maintenance therapy);
9) Discontinuing secondary prophylaxis after immune reconstitution; and
10) Special considerations during pregnancy.

Recommendations are rated using a revised version of the previous rating system (see Rating System for Prevention and Treatment Recommendations below) and accompanied, as needed, by explanatory text that

reviews the evidence and the working group's assessment. In this system, the letters A, B, or C signify the strength of the recommendation for or against a preventive or therapeutic measure, and Roman numerals I, II, or III indicate the quality of evidence supporting the recommendation. In cases where there were no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected persons existed that could plausibly guide management of HIV-infected patients, the recommendation is rated as a II or III but is assigned A, B, or C depending on the strength of the recommendation.

Rating System for Prevention and Treatment Recommendations

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

This document also includes tables in each OI section pertinent to the prevention and treatment of OIs, as well as eight summary tables at the end of the document (Tables 1–8), a figure that includes immunization recommendations, and an appendix that summarizes recommendations pertinent to preventing exposure to opportunistic pathogens, including preventing exposure to STIs (Appendix A).

Special Considerations Regarding Pregnancy

No large studies have been conducted concerning the epidemiology or manifestations of HIV-associated OIs among pregnant women. No data demonstrate that the spectrum of OIs differs from that among non-pregnant women with comparable CD4+ counts.

Physiologic changes during pregnancy can complicate the recognition of OIs and complicate treatment due to changes in pharmacokinetic parameters, which may influence optimal dosing for drugs used for prevention or treatment of OI. Factors to consider include the following:[61]

- Increased cardiac output by 30% to 50% with concomitant increase in glomerular filtration rate and renal clearance.
- Increased plasma volume by 45% to 50% while red cell mass increases only by 20% to 30%, leading to dilutional anemia.
- Tidal volume and pulmonary blood flow increase, possibly leading to increased absorption of aerosolized medications. The tidal volume increase of 30% to 40% should be considered if ventilator assistance is required.
- Placental transfer of drugs, increased renal clearance, altered gastrointestinal absorption, and metabolism by the fetus that might affect maternal drug levels.
- Limited pharmacokinetic data are available; use usual adult doses based on current weight, monitor levels if available, and consider the need to increase doses if the patient is not responding as expected.

Non-invasive imaging, including imaging that may expose a patient to radiation, is an important component of OI diagnosis. Fetal risk is not increased with cumulative radiation doses below 5 rads; the majority of imaging studies result in radiation exposure to the fetus that is lower than the 5-rad recommended limit. In humans, the primary risks associated with high-dose radiation exposure are growth restriction, microcephaly,

and developmental disabilities. The most vulnerable period is 8 to 15 menstrual weeks of gestation, with minimal risk before 8 weeks and after 25 weeks. The apparent threshold for development of mental retardation is 20 to 40 rads, with risk of more serious mental retardation increasing linearly with increasing exposure above this level. Among children, risk for carcinogenesis might be increased approximately 1 per 1000 or less per rad of in utero radiation exposure.[62] Therefore, pregnancy should not preclude usual diagnostic evaluation when an OI is suspected.[63] Abdominal shielding should be used when feasible to further limit radiation exposure to the fetus. Experience with use of magnetic resonance imaging (MRI) in pregnancy is limited, but no adverse fetal effects have been noted.[64]

Other procedures necessary for diagnosis of suspected OIs should be performed in pregnancy as indicated for non-pregnant patients. A pregnant woman who is >20 weeks of gestation should not lie flat on her back but should have her right hip elevated with a wedge to displace the uterus off the great vessels and prevent supine hypotension. Oxygenation should be monitored when pregnant patients are positioned such that ventilation or perfusion might be compromised.

In the United States, pregnancy is an indication to start antiretroviral therapy if the HIV-infected woman is not already on therapy. A decision to defer therapy based on a current or recent OI should be made on the same basis as for non-pregnant individuals supplemented by consultation with the obstetrician regarding factors unique to each individual pregnancy.

After first-trimester exposure to agents of uncertain teratogenic potential, including many of the anti-infective agents described in this guideline, an ultrasound should be conducted every 4 to 6 weeks in the third trimester to assess fetal growth and fluid volume, with antepartum testing if growth lag or decreased fluid are noted.

References

1. Kaplan JE, Masur H, Holmes KK, et al. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: introduction. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *Clin Infect Dis*. Aug 1995;21 Suppl 1:S1-11. Available at http://www.ncbi.nlm.nih.gov/pubmed/8547495.
2. Kaplan JE, Masur H, Jaffe HW, Holmes KK. Reducing the impact of opportunistic infections in patients with HIV infection. New guidelines. *JAMA*. Jul 26 1995;274(4):347-348. Available at http://www.ncbi.nlm.nih.gov/pubmed/7609267.
3. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis*. Jul 1 2006;194(1):11-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/16741877.
4. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. Mar 26 1998;338(13):853-860. Available at http://www.ncbi.nlm.nih.gov/pubmed/9516219.
5. Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA*. Nov 4 1998;280(17):1497-1503. Available at http://www.ncbi.nlm.nih.gov/pubmed/9809730.
6. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR. CDC surveillance summaries: Morbidity and mortality weekly report. CDC surveillance summaries / Centers for Disease Control*. Apr 16 1999;48(2):1-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/12412613.
7. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. Nov 28 1998;352(9142):1725-1730. Available at http://www.ncbi.nlm.nih.gov/pubmed/9848347.
8. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. *AIDS*. Sep 10 1999;13(13):1687-1695. Available at http://www.ncbi.nlm.nih.gov/pubmed/10509570.
9. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1

disease progression: results from the EuroSIDA study. *Ann Intern Med*. Apr 6 1999;130(7):570-577. Available at http://www.ncbi.nlm.nih.gov/pubmed/10189326.

10. Dore GJ, Li Y, McDonald A, Ree H, Kaldor JM, National HIVSC. Impact of highly active antiretroviral therapy on individual AIDS-defining illness incidence and survival in Australia. *J Acquir Immune Defic Syndr*. Apr 1 2002;29(4):388-395. Available at http://www.ncbi.nlm.nih.gov/pubmed/11917244.
11. Centers for Disease C, Prevention. Vital signs: HIV prevention through care and treatment—United States. *MMWR Morb Mortal Wkly Rep*. Dec 2 2011;60(47):1618-1623. Available at http://www.ncbi.nlm.nih.gov/pubmed/22129997.
12. Campsmith ML, Rhodes PH, Hall HI, Green TA. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. *J Acquir Immune Defic Syndr*. Apr 2010;53(5):619-624. Available at http://www.ncbi.nlm.nih.gov/pubmed/19838124.
13. Seal PS, Jackson DA, Chamot E, et al. Temporal trends in presentation for outpatient HIV medical care 2000-2010: implications for short-term mortality. *J Gen Intern Med*. Jul 2011;26(7):745-750. Available at http://www.ncbi.nlm.nih.gov/pubmed/21465301.
14. Perbost I, Malafronte B, Pradier C, et al. In the era of highly active antiretroviral therapy, why are HIV-infected patients still admitted to hospital for an inaugural opportunistic infection? *HIV Med*. Jul 2005;6(4):232-239. Available at http://www.ncbi.nlm.nih.gov/pubmed/16011527.
15. Palacios R, Hidalgo A, Reina C, de la Torre M, Marquez M, Santos J. Effect of antiretroviral therapy on admissions of HIV-infected patients to an intensive care unit. *HIV Med*. Apr 2006;7(3):193-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/16494634.
16. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. Mar 15 2011;52(6):793-800. Available at http://www.ncbi.nlm.nih.gov/pubmed/21367734.
17. Greenberg AE, Hader SL, Masur H, Young AT, Skillicorn J, Dieffenbach CW. Fighting HIV/AIDS in Washington, D.C. *Health affairs*. Nov-Dec 2009;28(6):1677-1687. Available at http://www.ncbi.nlm.nih.gov/pubmed/19887408.
18. Gebo KA, Fleishman JA, Reilly ED, Moore RD, Network HIVR. High rates of primary Mycobacterium avium complex and Pneumocystis jiroveci prophylaxis in the United States. *Medical care*. Sep 2005;43(9 Suppl):III23-30. Available at http://www.ncbi.nlm.nih.gov/pubmed/16116306.
19. Bonnet F, Lewden C, May T, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. *Scandinavian journal of infectious diseases*. 2005;37(6-7):482-487. Available at http://www.ncbi.nlm.nih.gov/pubmed/16089023.
20. Teshale EH, Hanson DL, Wolfe MI, et al. Reasons for lack of appropriate receipt of primary Pneumocystis jiroveci pneumonia prophylaxis among HIV-infected persons receiving treatment in the United States: 1994-2003. *Clin Infect Dis*. Mar 15 2007;44(6):879-883. Available at http://www.ncbi.nlm.nih.gov/pubmed/17304464.
21. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. *J Acquir Immune Defic Syndr*. Dec 15 2005;40(5):609-616. Available at http://www.ncbi.nlm.nih.gov/pubmed/16284539.
22. Betz ME, Gebo KA, Barber E, et al. Patterns of diagnoses in hospital admissions in a multistate cohort of HIV-positive adults in 2001. *Medical care*. Sep 2005;43(9 Suppl):III3-14. Available at http://www.ncbi.nlm.nih.gov/pubmed/16116304.
23. Moorman AC, Buchacz K, Richardson JT, al. e. Temporal trends in hospitalizations and hospital-associated diagnoses in the HIV Outpatient Study (HOPS) 1994-2002. In: XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. Abstract MOPE0071.
24. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994-1998. *J Infect Dis*. Oct 1 2002;186(7):1023-1027. Available at http://www.ncbi.nlm.nih.gov/pubmed/12232845.
25. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. Sep 2006;43(1):27-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/16878047.
26. Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS*. Mar 21 2006;20(5):741-749. Available at http://www.ncbi.nlm.nih.gov/pubmed/16514305.

27. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994-2005. *AIDS*. Jul 11 2008;22(11):1345-1354. Available at http://www.ncbi.nlm.nih.gov/pubmed/18580614.

28. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. Jun 19 2010;24(10):1549-1559. Available at http://www.ncbi.nlm.nih.gov/pubmed/20502317.

29. Lawn SD, Butera ST, Folks TM. Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. *Clin Microbiol Rev*. Oct 2001;14(4):753-777, table of contents. Available at http://www.ncbi.nlm.nih.gov/pubmed/11585784.

30. Toossi Z, Mayanja-Kizza H, Hirsch CS, et al. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. *Clinical and experimental immunology*. Feb 2001;123(2):233-238. Available at http://www.ncbi.nlm.nih.gov/pubmed/11207653.

31. Sadiq ST, McSorley J, Copas AJ, et al. The effects of early syphilis on CD4 counts and HIV-1 RNA viral loads in blood and semen. *Sexually transmitted infections*. Oct 2005;81(5):380-385. Available at http://www.ncbi.nlm.nih.gov/pubmed/16199736.

32. Bentwich Z. Concurrent infections that rise the HIV viral load. *Journal of HIV Therapy*. Aug 2003;8(3):72-75. Available at http://www.ncbi.nlm.nih.gov/pubmed/12951545.

33. Kublin JG, Patnaik P, Jere CS, et al. Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet*. Jan 15-21 2005;365(9455):233-240. Available at http://www.ncbi.nlm.nih.gov/pubmed/15652606.

34. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science*. Dec 8 2006;314(5805):1603-1606. Available at http://www.ncbi.nlm.nih.gov/pubmed/17158329.

35. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. Mar 30 2000;342(13):921-929. Available at http://www.ncbi.nlm.nih.gov/pubmed/10738050.

36. DiRienzo AG, van Der Horst C, Finkelstein DM, Frame P, Bozzette SA, Tashima KT. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. *AIDS research and human retroviruses*. Jan 20 2002;18(2):89-94. Available at http://www.ncbi.nlm.nih.gov/pubmed/11839141.

37. Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet*. May 1 1999;353(9163):1469-1475. Available at http://www.ncbi.nlm.nih.gov/pubmed/10232312.

38. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. Sep 18 1997;337(12):801-808. Available at http://www.ncbi.nlm.nih.gov/pubmed/9295239.

39. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at http://www.ncbi.nlm.nih.gov/pubmed/10232311.

40. Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet*. Nov 20-26 2004;364(9448):1865-1871. Available at http://www.ncbi.nlm.nih.gov/pubmed/15555666.

41. Centers for Disease C. Guidelines for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. Jun 16 1989;38 Suppl 5(Suppl 5):1-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/2524643.

42. Masur H. Recommendations on prophylaxis and therapy for disseminated Mycobacterium avium complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for Mycobacterium avium Complex. *N Engl J Med*. Sep 16 1993;329(12):898-904. Available at http://www.ncbi.nlm.nih.gov/pubmed/8395019.

43. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *MMWR Recomm Rep*. Jul 14 1995;44(RR-8):1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/7565547.

44. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *MMWR Recomm Rep*. Jun 27 1997;46(RR-12):1-46. Available at http://www.ncbi.nlm.nih.gov/pubmed/9214702.

45. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep*. Aug 20 1999;48(RR-10):1-59, 61-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/10499670.

46. Kaplan JE, Masur H, Holmes KK, Usphs, Infectious Disease Society of A. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recomm Rep*. Jun 14 2002;51(RR-8):1-52. Available at http://www.ncbi.nlm.nih.gov/pubmed/12081007.

47. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *Clin Infect Dis*. Aug 1995;21 Suppl 1:S32-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/8547510.

48. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. US Public Health Services/Infectious Diseases Society of America. *Clin Infect Dis*. Oct 1997;25 Suppl 3:S313-335. Available at http://www.ncbi.nlm.nih.gov/pubmed/9356832.

49. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Clin Infect Dis*. Apr 2000;30 Suppl 1:S29-65. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770913.

50. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *Ann Intern Med*. Feb 1 1996;124(3):349-368. Available at http://www.ncbi.nlm.nih.gov/pubmed/8554235.

51. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Ann Intern Med*. Nov 15 1997;127(10):922-946. Available at http://www.ncbi.nlm.nih.gov/pubmed/9382373.

52. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV: Part I. Prevention of exposure. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. *American family physician*. Sep 1 1997;56(3):823-834. Available at http://www.ncbi.nlm.nih.gov/pubmed/9301575.

53. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV: part I. Prevention of exposure. *American family physician*. Jan 1 2000;61(1):163-174. Available at http://www.ncbi.nlm.nih.gov/pubmed/10643957.

54. Antiretroviral therapy and medical management of pediatric HIV infection and 1997 USPHS/IDSA report on the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Pediatrics*. Oct 1998;102(4 Pt 2):999-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/9826994.

55. Kaplan JE, Masur H, Jaffe HW, Holmes KK. Preventing opportunistic infections in persons infected with HIV: 1997 guidelines. *JAMA*. Jul 23-30 1997;278(4):337-338. Available at http://www.ncbi.nlm.nih.gov/pubmed/9228443.

56. Brooks JT, Kaplan JE, Masur H. What's new in the 2009 US guidelines for prevention and treatment of opportunistic infections among adults and adolescents with HIV? *Top HIV Med*. Jul-Aug 2009;17(3):109-114. Available at http://www.ncbi.nlm.nih.gov/pubmed/19675369.

57. Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR Recomm Rep*. Dec 17 2004;53(RR-15):1-112. Available at http://www.ncbi.nlm.nih.gov/pubmed/15841069.

58. Mofenson LM, Oleske J, Serchuck L, et al. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR Recomm Rep*. Dec 3 2004;53(RR-14):1-92. Available at http://www.ncbi.nlm.nih.gov/pubmed/15577752.

59. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine

Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. Apr 10 2009;58(RR-4):1-207; quiz CE201-204. Available at http://www.ncbi.nlm.nih.gov/pubmed/19357635.

60. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. Sep 4 2009;58(RR-11):1-166. Available at http://www.ncbi.nlm.nih.gov/pubmed/19730409.
61. Cruickshank DP, Wigton TR, Hays PM. Maternal physiology in pregnancy. In: Gabbe SG, Neibyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies. New York, NY: Churchchill Livingstone, 1996.
62. ACOG Committee on Obstetric Practice. ACOG Committee Opinion. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. *Obstet Gynecol*. Sep 2004;104(3):647-651. Available at http://www.ncbi.nlm.nih.gov/pubmed/15339791.
63. Toppenberg KS, Hill DA, Miller DP. Safety of radiographic imaging during pregnancy. *American family physician*. Apr 1 1999;59(7):1813-1818, 1820. Available at http://www.ncbi.nlm.nih.gov/pubmed/10208701.
64. Adelstein SJ. Administered radionuclides in pregnancy. *Teratology*. Apr 1999;59(4):236-239. Available at http://www.ncbi.nlm.nih.gov/pubmed/10331526.

Pneumocystis Pneumonia (Last updated September 10, 2015; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a ubiquitous organism that is classified as a fungus but also shares biologic characteristics with protozoa. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the *Pneumocystis* that infects rats, and *P. jirovecii* refers to the distinct species that infects humans. The abbreviation PCP is still used to designate *Pneumocystis* pneumonia. Initial infection with *P. jirovecii* usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* by ages 2 to 4 years.[1]

Rodent studies and case clusters in immunosuppressed patients suggest that Pneumocystis spreads by the airborne route. Disease probably occurs by new acquisition of infection and by reactivation of latent infection.[2-11] Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of patients with AIDS;[12] the course of treated PCP was associated with a 20% to 40% mortality rate in individuals with profound immunosuppression. Approximately 90% of PCP cases occurred in patients with CD4 T-lymphocyte (CD4 cell) counts <200 cells/mm^3. Other factors associated with a higher risk of PCP included CD4 cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA levels.[13,14]

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is <1 case per 100 person-years.[15] Most cases occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV,[16] and in those with advanced immunosuppression (CD4 counts <100 cells/mm^3).[17]

Clinical Manifestations

In HIV-infected patients, the most common manifestations of PCP are subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed in patients who are not infected with HIV is less common.[18,19]

In mild cases, pulmonary examination usually is normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.[19] Oral thrush is a common co infection. Fever is apparent in most cases and may be the predominant symptom in some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.[20]

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen [pO_2] ≥70 mm Hg or alveolar-arterial O_2 difference, [A-a] DO_2 <35 mm Hg) to moderate ([A-a] DO_2 ≥35 and <45 mm Hg) to severe ([A-a] DO_2 ≥45 mm Hg). Oxygen desaturation with exercise is often abnormal but is non-specific.[21] Elevation of lactate dehydrogenase levels to >500 mg/dL is common but non-specific.[22] Chest radiograph typically demonstrates diffuse, bilateral, symmetrical interstitial infiltrates emanating from the hila in a butterfly pattern;[19] however, a chest radiograph may be normal in patients with early disease.[23] Atypical radiographic presentations also occur, such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, and pneumothorax. Spontaneous pneumothorax in a patient with HIV infection should raise the suspicion of PCP.[24,25] Cavitation, intrathoracic adenopathy, and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis. Approximately 13% to 18% of patients with documented PCP have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma (KS), or bacterial pneumonia.[26,27]

Thin-section computed tomography (CT) demonstrating patchy ground-glass attenuation[28,29] increases the

likelihood that a diagnostic study, such as bronchoscopy, will demonstrate PCP in patients with mild-to-moderate symptoms and normal chest radiograph and, therefore, may be useful as an adjunct.

Diagnosis

Because clinical presentation, blood tests, and chest radiographs are not pathognomonic for PCP, and because the organism cannot be cultivated routinely, histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples[18,26,27,30] is required for a definitive diagnosis. Spontaneously expectorated sputum has low sensitivity and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both the cystic and trophic forms but do not stain the cyst wall; Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Some laboratories prefer direct immunofluorescent staining. Previous studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: induced sputum <50% to >90% (the sensitivity depends on the pathogen load and specimen quality, while the specificity depends on the experience of the microbiologist or pathologist), bronchoscopy with BAL 90% to 99%, transbronchial biopsy 95% to 100%, and open lung biopsy 95% to 100%.

Polymerase chain reaction (PCR) is an emerging method for diagnosing PCP.[31] The sensitivity of PCR for bronchoalveolar lavage appears to be high; the ability of PCR to distinguish colonization from disease is less clear.[31-34] 1,3ß-D-glucan (a component of fungal cell walls) may be elevated in patients with PCP, but the assay's sensitivity and specificity for establishing a PCP diagnosis are problematic,[35,36] and other fungal diseases can produce elevation.

Because certain processes produce similar clinical manifestations, a specific diagnosis of PCP should be sought rather than relying on a presumptive diagnosis, especially in patients with moderate-to-severe disease. Treatment can be initiated before making a definitive diagnosis because organisms persist in clinical specimens for days or weeks after effective therapy is initiated.[30]

Preventing Exposure

Pneumocystis can be quantified in the air near patients with PCP,[37] and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients.[5-11,38] Although these strongly suggest that high-risk patients without PCP may benefit from isolation from other patients with known PCP infection, data are insufficient to support isolation as standard practice **(CIII)**.

Preventing Disease

Indication for Primary Prophylaxis

HIV-infected adults and adolescents, including pregnant women and those on ART, should receive chemoprophylaxis against PCP if they have CD4 counts <200 cells/mm^3 **(AI)** or a history of oropharyngeal candidiasis **(AII)**.[12,13,39] Persons who have a CD4 cell percentage of <14% or a history of an AIDS-defining illness, but who do not otherwise qualify, should be considered for prophylaxis **(BII)**.[12,13,39] Initiation of chemoprophylaxis at CD4 counts between 200 and 250 cells/mm^3 also should be considered when frequent monitoring of CD4 counts, such as every 3 months, is impossible **(BII)**.[13] Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP **(AII)**.[40]

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent **(AI)**.[39,41-43] One double-strength tablet daily is the preferred regimen **(AI)**, but one single-strength tablet daily[43] also is effective and may be better tolerated than the double-strength tablet **(AI)**. One double-strength tablet three times weekly also is effective **(BI)**.[44] TMP-SMX at a dose of one double-strength tablet daily confers cross protection against toxoplasmosis[45] and many respiratory bacterial infections.[41,46] Lower doses of TMP-SMX likely also confer such protection. TMP-SMX chemoprophylaxis should be continued, if clinically feasible, in patients who have non life threatening adverse reactions. In those who discontinue TMP-SMX because of a mild

adverse reaction, re-institution should be considered after the reaction has resolved **(AII)**. Therapy should be permanently discontinued (with no rechallenge) in patients with life threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN) **(AIII)**. Patients who have experienced adverse events, including fever and rash, may better tolerate re-introduction of the drug if the dose is gradually increased (desensitization) according to published regimens **(BI)**[47,48] or if TMP-SMX is given at a reduced dose or frequency **(CIII)**. As many as 70% of patients can tolerate such re-institution of therapy.[46]

For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone **(BI)**,[41] dapsone plus pyrimethamine plus leucovorin **(BI)**,[49-51] aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) **(BI)**,[42] and atovaquone **(BI)**.[52,53] Atovaquone is as effective as aerosolized pentamidine[52] or dapsone[53] but substantially more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin **(BI)**,[49-51] or atovaquone with or without pyrimethamine plus leucovorin **(CIII)**.

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine.

Oral pyrimethamine plus sulfadoxine also has activity against PCP.[54-56] However, this combination is associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,[57] and the long half-life of both pyrimethamine and sulfadoxine results in delayed clearance when the drug is stopped. Because TMP-SMX has superior safety, widespread availability, and is low cost, oral pyrimethamine plus sulfadoxine should **not** be used in the United States **(AIII)**.

The following regimens cannot be recommended as alternatives because data regarding their efficacy for PCP prophylaxis are insufficient:

- Aerosolized pentamidine administered by nebulization devices other than the Respirgard II nebulizer
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine

Clinicians can consider using these agents, however, in situations in which the recommended agents cannot be administered or are not tolerated **(CIII)**.

Discontinuing Primary Prophylaxis

Primary *Pneumocystis* prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4 counts from <200 cells/mm^3 to ≥200 cells/mm^3 for >3 months **(AI)**. In observational and randomized studies supporting this recommendation, most patients had CD4 counts >200 cells/mm^3 for more than 3 months before discontinuing PCP prophylaxis.[58-67] The median CD4 count at the time prophylaxis was discontinued was >300 cells/mm^3, most patients had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 to 19 months.

Discontinuing primary prophylaxis in these patients is recommended because its preventive benefits are limited to PCP, toxoplasmosis, and bacterial infections;[60,66] stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens. Prophylaxis should be reintroduced if the CD4 count decreases to <200 cells/mm^3 **(AIII)**.

A combined analysis of 12 European cohorts[68] and a case series[69] found a low incidence of PCP in patients with CD4 counts between 100 and 200 cells/mm^3, who were receiving ART and had HIV plasma viral loads <50 to 400 copies/mL, and who had stopped or never received PCP prophylaxis, suggesting that primary PCP prophylaxis can be safely discontinued in selected patients with CD4 counts 100 to 200 cells/mm^3 and HIV plasma RNA levels below limits of detection with commercial assays. Data on which to base recommendations for this approach are inadequate, but some experts believe it is reasonable and recommend it for their patients.

Treating Disease

TMP-SMX is the treatment of choice for PCP **(AI)**.[70,71] The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because efficacy is questionable and some evidence exists for a higher failure rate **(AII)**.[72] Oral outpatient therapy with TMP-SMX is highly effective in patients with mild-to-moderate disease **(AI)**.[71]

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.[73-76] Patients who have PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX **(BIII)**.

Patients with documented or suspected PCP and moderate-to-severe disease, defined by room air pO_2 <70 mm Hg or Alveolar-arterial O_2 gradient ≥35 mm Hg, should receive adjunctive corticosteroids as early as possible and certainly within 72 hours after starting specific PCP therapy **(AI)**.[77-82] The benefits of starting steroids later are unclear, but most clinicians would use them in such circumstances for patients with moderate-to-severe disease **(BIII)**. Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone and TMP **(BI)**,[71,83] which may have efficacy similar to TMP-SMX and fewer side effects, but is less convenient because of the number of pills; primaquine plus clindamycin **(BI)**[84-86] (the clindamycin component can be administered intravenously [IV] for more severe cases, but primaquine is only available orally); and atovaquone suspension **(BI)**,[53,58,70,87] which is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects. Whenever possible, patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before primaquine or dapsone is administered.

Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or IV pentamidine **(AI)**.[86,88,89] Some clinicians prefer clindamycin-primaquine because of its higher degree of efficacy and lesser toxicity compared with pentamidine.[86,90-92]

Aerosolized pentamidine **should not** be used to treat PCP because its efficacy is limited and it is associated with more frequent relapse **(AI)**.[88,93,94] Trimetrexate is no longer commercially available.

The recommended duration of therapy for PCP is 21 days **(AII)**.[18] The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of pulmonary illness, degree of immunodeficiency, timing of initiation of therapy and comorbidities.

The overall prognosis remains poor for patients who have such severe hypoxemia that admission to an intensive care unit (ICU) is necessary. However, in recent years, such patients have had much better survival than in the past, perhaps because of better management of comorbidities and better supportive care.[95-98] Because long-term survival is possible for patients in whom ART is effective, individuals with AIDS and severe PCP should be offered ICU admission or mechanical ventilation if their functional status is such that it would be appropriate, just as with HIV-uninfected patients **(AII)**.

Special Consideration with Regards to Starting ART

In patients not on ART, ART should be initiated, when possible, within 2 weeks of diagnosis of PCP **(AI)**. In a randomized controlled trial of 282 patients with opportunistic infections (OIs) other than TB, 63% of whom had PCP, a significantly lower incidence of AIDS progression or death (a secondary study endpoint) was seen in subjects randomized to early (median 12 days after initiation of therapy for OI) versus deferred initiation of ART (median 45 days).[99] Of note, no patients with PCP and respiratory failure requiring intubation were enrolled in the study.[99] Paradoxical immune reconstitution inflammatory syndrome (IRIS) has been reported following PCP.[100] Most cases have occurred within weeks of the episode of PCP; symptoms include fever and

recurrence or exacerbation of pulmonary symptoms including cough and shortness of breath. Although IRIS in the setting of PCP has only rarely been life threatening,[101] patients should be closely followed for recurrence of symptoms after initiation of ART. Management of PCP-associated IRIS is not well defined; some experts would consider corticosteroids in patients with respiratory deterioration if other causes are ruled out.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Careful monitoring during anti-PCP therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity. PCP prophylaxis should be initiated immediately upon completion of therapy and maintained until the CD4 count is >200 cells/mm^3 for at least 3 months.

In patients with AIDS, rates of adverse reaction to TMP-SMX are high (20%–85%).[70,71,83,85,89,102-106] Common adverse effects are rash (30%–55%) (including Stevens-Johnson syndrome), fever (30%–40%), leukopenia (30%–40%), thrombocytopenia (15%), azotemia (1%–5%), hepatitis (20%), and hyperkalemia. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued **(AIII)**. Rashes often can be "treated through" with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone;[71,83] azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine;[87-89,105] anemia, rash, fever, and diarrhea with primaquine and clindamycin;[71,84,85] and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.[70,104]

Managing Treatment Failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases (ABGs) after at least 4 to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease. No convincing clinical trials exist on which to base recommendations for the management of treatment failure attributed to lack of drug efficacy. Clinicians should wait at least 4 to 8 days before switching therapy for lack of clinical improvement **(BIII)**. In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause of clinical failure;[26,27] bronchoscopy with BAL should be strongly considered to evaluate for this possibility, even if the procedure was conducted before initiating therapy.

Treatment failure attributed to treatment-limiting toxicities occurs in up to one-third of patients.[71] Switching to another regimen is the appropriate management for treatment-related toxicity **(BII)**. When TMP-SMX is not effective or cannot be used for moderate-to-severe disease because of toxicity, the common practice is to use parenteral pentamidine or oral primaquine combined with intravenous clindamycin **(BII)**.[85,89,106] For mild disease, atovaquone is a reasonable alternative **(BII)**. Although a meta-analysis, systematic review, and cohort study concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy,[86,91,92] no prospective clinical trials have evaluated the optimal approach to patients who experience a therapy failure with TMP-SMX.

Preventing Recurrence

When to Start Secondary Prophylaxis

Patients who have a history of PCP should be given chemoprophylaxis for life with TMP-SMX (i.e., secondary prophylaxis or chronic maintenance therapy) unless immune reconstitution occurs as a result of ART (see below) **(AI)**.[107] For patients who are intolerant of TMP-SMX, the alternatives are dapsone, dapsone

combined with pyrimethamine, atovaquone, and aerosolized pentamidine.

When to Stop Secondary Prophylaxis

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from <200 to ≥200 cells mm^3 for >3 months as a result of ART **(AII)**. Reports from observational studies[59,65,108,109] and from two randomized trials[66,110] and a combined analysis of eight European cohorts being followed prospectively[111] support this recommendation. In these studies, patients responded to ART with an increase in CD4 counts to ≥200 cells/mm^3 for >3 months. At the time prophylaxis was discontinued, the median CD4 count was >300 cells/mm^3 and most patients had a CD4 cell percentage >14%. Most patients had sustained suppression of plasma HIV RNA levels below the limits of detection for the assay employed; the longest follow-up was 40 months. Prophylaxis should be reintroduced if the CD4 count decreases to <200 cells/mm^3 **(AIII)**.

If an episode of PCP occurs at a CD4 count ≥200 cells/mm^3, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART **(BIII)**.

Special Considerations During Pregnancy

PCP diagnostic considerations for pregnant women are the same as for women who are not pregnant.

Indications for therapy are the same as for non-pregnant women. Some data suggest an increased risk of PCP-associated mortality in pregnancy compared with non-pregnant adults, although there are no large, well-controlled studies evaluating the impact of pregnancy on PCP outcomes.[112]

The preferred initial therapy during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX **(AI)**.[113] In case-control studies, trimethoprim has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after first-trimester exposure.[114-116] One small study reported an increased risk of birth defects in infants born to women receiving ARV drugs and folate antagonists, primarily trimethoprim, whereas no increase was observed among those with exposure to either an ARV drug or a folate antagonist alone.[117] Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP still should be treated with TMP-SMX because of its considerable benefit **(AIII)**.

Although folic acid supplementation of 0.4 mg/day is routinely recommended for all pregnant women,[118] there are no trials evaluating whether supplementation at higher levels (such as the 4 mg/day recommended for pregnant women with a previous infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use. Epidemiologic data do suggest, however, that folic acid supplementation may reduce the risk of congenital anomalies.[115,116] In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received 6 mg/day (odds ratio [OR] 1.24; 95% confidence interval [CI]: 0.94-1.62).[119] Although the risk of multiple congenital anomalies associated with TMP-SMX use persisted with supplemental folic acid, the OR decreased from 6.4 (TMP-SMX, no folic acid) to 1.9 (TMP-SMX plus folic acid). As such, clinicians can consider giving supplemental folic acid (>0.4 mg/day routinely recommended) to women in their first trimester who are on TMP-SMX **(BIII)**. On the other hand, a randomized, controlled trial demonstrated that adding folinic acid to TMP-SMX treatment for PCP was associated with an increased risk of therapeutic failure and death.[72] In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent folinic acid use.[120] Therefore, if supplemental folic acid (>0.4 mg/day routinely recommended) is to be given, its use should be limited to the first trimester during the teratogenic window **(AIII)**. Whether or not a woman receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 to 20 weeks to assess fetal anatomy **(BIII)**.

A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of kernicterus and mortality, specifically kernicterus, compared with infants who received oxytetracycline.[121] Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, although no published studies to date link late third-trimester exposure to either drug with neonatal death or kernicterus.

Adjunctive corticosteroid therapy should be used to improve the mother's treatment outcome as indicated in nonpregnant adults **(AIII)**.[122-125] Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient ≥35 mm Hg, should receive adjunctive corticosteroids as early as possible. A systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4 increase in odds of delivering a baby with a cleft palate.[126] On the other hand, other large population-based studies have not found an association between maternal use of corticosteroids and congenital anomalies.[127,128] Corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, glucose intolerance/gestational diabetes, and infection.[129] Maternal glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk of glucose intolerance is increased **(AIII)**. Moreover, women receiving 20 mg/day of prednisone (or its dosing equivalent for other exogenous corticosteroids) for more than 3 weeks may have a suppressed hypothalamic-pituitary-adrenal (HPA) axis and consideration should be given to the use of stress-dose steroids during delivery **(BIII)**. HPA axis suppression is rarely seen among neonates born to women on chronic corticosteroids during pregnancy.

Alternative therapeutic regimens for mild-to-moderate disease include dapsone and TMP, primaquine plus clindamycin, atovaquone suspension, and IV pentamidine.

Dapsone appears to cross the placenta.[130,131] It has been used safely over the past several decades to treat leprosy, malaria, and various dermatologic conditions during pregnancy.[131,132] Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of hemolytic anemia.[133]

Clindamycin, which appears to cross the placenta, is a Food and Drug Administration (FDA) Pregnancy Category B medication and considered safe for use throughout pregnancy.

Primaquine generally is not used in pregnancy because of the risk of maternal hemolysis. As with dapsone, there is potential risk of hemolytic anemia in exposed fetuses with G6PD deficiency. The degree of intravascular hemolysis appears to be associated with both dose of primaquine and severity of G6PD deficiency.[134]

Data on atovaquone in humans are limited but preclinical studies have not demonstrated toxicity.[134]

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.[135]

Pneumonia during pregnancy increases rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions **(BIII)**.

Chemoprophylaxis for PCP should be administered to pregnant women the same as for other adults and adolescents **(AIII)**. TMP-SMX is the recommended prophylactic agent. Given theoretical concerns about possible teratogenicity associated with first-trimester drug exposures, health care providers may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during this period **(CIII)** rather than withholding chemoprophylaxis.

Preconception Care

Clinicians who are providing pre-conception care for HIV-infected women receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued; that is, until the CD4 cell count is ≥200 cells/mm^3 for 3 months **(BIII)**.

Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia (PCP)

Preventing 1st Episode of PCP (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <200 cells/mm^3 **(AI)** *or*
- Oropharyngeal candidiasis **(AII)** *or*
- CD4% <14% **(BII)** *or*
- History of AIDS-defining illness **(BII)** *or*
- CD4 count >200 but <250 cells/mm^3 and if CD4 cell count monitoring (e.g., every 3 months) is not possible **(BII)**.

Note—Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP **(AII)**.

Preferred Therapy:

- TMP-SMX, 1 DS PO daily[a] **(AI)** *or*
- TMP-SMX, 1 SS PO daily[a] **(AI)**.

Alternative Therapy:

- TMP-SMX 1 DS PO three times weeklya **(BI)** *or*
- Dapsone[b,c] 100 mg PO daily or 50 mg PO BID **(BI)** *or*
- Dapsone[b] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)** *or*
- (Dapsone[b] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)** *or*
- Aerosolized pentamidine[c] 300 mg via Respigard II™ nebulizer every month **(BI)** *or*
- Atovaquone 1500 mg PO daily with food **(BI)** *or*
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food **(CIII)**.

Indication for Discontinuing Primary Prophylaxis:

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for at least 3 months in response to ART **(AI)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <200 cells/mm^3 **(AIII)**

Treating PCP

Note—Patients who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX **(BIII)**.

For Moderate to Severe PCP—Total Duration = 21 Days (AII):

Preferred Therapy:

- TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given q6h or q8h **(AI)**, may switch to PO after clinical improvement **(AI)**.

Alternative Therapy:

- Pentamidine 4 mg/kg IV once daily infused over at least 60 minutes **(AI)**; may reduce the dose to 3 mg/kg IV once daily because of toxicities **(BI)** *or*
- Primaquine[b] 30 mg (base) PO once daily + (Clindamycin [IV 600 q6h or 900 mg q8h] or [PO 450 mg q6h or 600 mg q8h]) **(AI)**.

**Adjunctive corticosteroid may be indicated in some moderate to severe cases (see indications and dosage recommendations below)

For Mild to Moderate PCP—Total Duration = 21 days (AII):

Preferred Therapy:

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day), given PO in 3 divided doses **(AI)** *or*
- TMP-SMX DS - 2 tablets TID **(AI)**.

Alternative Therapy:

- Dapsone[b] 100 mg PO daily + TMP 15 mg/kg/day PO (3 divided doses) **(BI)** *or*
- Primaquine[b] 30 mg (base) PO daily + Clindamycin PO (450 mg q6h or 600 mg q8h) **(BI)** *or*
- Atovaquone 750 mg PO BID with food **(BI)**

Adjunctive Corticosteroids:

For Moderate to Severe PCP Based on the Following Criteria ***(AI)****:*

- PaO_2 <70 mmHg at room air *or*
- Alveolar-arterial O_2 gradient ≥35 mmHg

Dosing Schedule:

Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) **(AI)**:

Days 1–5aily	40 mg PO BID
Days 6–10	40 mg PO daily
Days 11–21	20 mg PO d

IV methylprednisolone can be given as 75% of prednisone dose

Preventing Subsequent Episode of PCP (Secondary Prophylaxis)

Indications for Initiating Secondary Prophylaxis:

- Prior PCP

Preferred Therapy:

- TMP-SMX, 1 DS PO daily[a] **(AI)** *or*
- TMP-SMX, 1 SS PO daily[a] **(AI)**.

Alternative Therapy:

- TMP-SMX 1 DS PO three times weekly[a] **(BI)** *or*
- Dapsone[b,c] 100 mg PO daily or 50 mg PO BID **(BI)** *or*
- Dapsone[b] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)** *or*
- (Dapsone[b] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)** *or*
- Aerosolized pentamidine[c] 300 mg via Respigard II™ nebulizer every month **(BI)** *or*
- Atovaquone 1500 mg PO daily with food **(BI)** *or*
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food **(CIII)**

Indications for Discontinuing Secondary Prophylaxis:

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for >3 months as a result of ART **(AII)** *or*
- If PCP diagnosed when CD4 count ≥200 cells/mm^3, prophylaxis should be continued for life regardless of CD4 cell count rise as a consequence of ART **(BIII)**.

Indications for Restarting Secondary Prophylaxis:

- CD4 count falls to <200 cells/mm^3 **(AIII)** *or*
- If PCP recurred at a CD4 count ≥200 cells/mm^3, lifelong prophylaxis should be administered **(BIII)**.

Other Considerations/Comments:

- For patients with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction has resolved **(AII)**. The dose can be increased gradually (desensitization) **(BI)** or given at a reduced dose or frequency **(CIII)**.
- Therapy should be permanently discontinued, with no rechallenge, in patients with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrolysis **(AIII)**.

[a] TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.

[b] Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. Alternative agent should be used if the patient is found to have G6PD deficiency.

[c] Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in patients who are seropositive for *Toxoplasma gondii*.

Acronyms: BID = twice daily; DS = double strength; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; q "n" h = every "n" hour; SS = single strength; TID = three times daily; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. Pifer LL, Hughes WT, Stagno S, Woods D. Pneumocystis carinii infection: evidence for high prevalence in normal and immunosuppressed children. *Pediatrics*. Jan 1978;61(1):35-41. Available at http://www.ncbi.nlm.nih.gov/pubmed/400818.
2. Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. Genetic variation among Pneumocystis carinii hominis isolates in recurrent pneumocystosis. *J Infect Dis*. Aug 1995;172(2):595-598. Available at http://www.ncbi.nlm.nih.gov/pubmed/7542688.
3. Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of Pneumocystis carinii pneumonia: analysis of person-to-person transmission by genotyping. *QJM*. Dec 1998;91(12):813-820. Available at http://www.ncbi.nlm.nih.gov/pubmed/10024946.
4. Huang L, Beard CB, Creasman J, et al. Sulfa or sulfone prophylaxis and geographic region predict mutations in the Pneumocystis carinii dihydropteroate synthase gene. *J Infect Dis*. Oct 2000;182(4):1192-1198. Available at http://www.ncbi.nlm.nih.gov/pubmed/10979917.
5. Sassi M, Ripamonti C, Mueller NJ, et al. Outbreaks of Pneumocystis pneumonia in 2 renal transplant centers linked to a single strain of Pneumocystis: implications for transmission and virulence. *Clin Infect Dis*. May 2012;54(10):1437-1444. Available at http://www.ncbi.nlm.nih.gov/pubmed/22431811.
6. de Boer MG, Kroon FP, le Cessie S, de Fijter JW, van Dissel JT. Risk factors for Pneumocystis jirovecii pneumonia in kidney transplant recipients and appraisal of strategies for selective use of chemoprophylaxis. *Transpl Infect Dis*. Dec 2011;13(6):559-569. Available at http://www.ncbi.nlm.nih.gov/pubmed/21689251.
7. Arichi N, Kishikawa H, Mitsui Y, et al. Cluster outbreak of Pneumocystis pneumonia among kidney transplant patients within a single center. *Transplant Proc*. Jan–Feb 2009;41(1):170-172. Available at http://www.ncbi.nlm.nih.gov/pubmed/19249506.
8. Gianella S, Haeberli L, Joos B, et al. Molecular evidence of interhuman transmission in an outbreak of Pneumocystis jirovecii pneumonia among renal transplant recipients. *Transpl Infect Dis*. Feb 2010;12(1):1-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/19744285.
9. Mori S, Cho I, Sugimoto M. A cluster of Pneumocystis jirovecii infection among outpatients with rheumatoid arthritis. *J Rheumatol*. Jul 2010;37(7):1547-1548. Available at http://www.ncbi.nlm.nih.gov/pubmed/20595296.
10. Schmoldt S, Schuhegger R, Wendler T, et al. Molecular evidence of nosocomial Pneumocystis jirovecii transmission among 16 patients after kidney transplantation. *J Clin Microbiol*. Mar 2008;46(3):966-971. Available at http://www.ncbi.nlm.nih.gov/pubmed/18216217.
11. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of Pneumocystis jiroveci pneumonia in renal transplant recipients: P. jiroveci is contagious to the susceptible host. *Transplantation*. Aug 15 2009;88(3):380-385. Available at http://www.ncbi.nlm.nih.gov/pubmed/19667941.
12. Phair J, Munoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. Jan 18 1990;322(3):161-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/1967190.
13. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary Pneumocystis carinii pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis*. Oct 1998;178(4):1126-1132. Available at http://www.ncbi.nlm.nih.gov/pubmed/9806044.
14. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS*. Sep 28 2001;15(14):1831-1836. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11579245.
15. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. Jun 19 2010;24(10):1549-1559. Available at http://www.ncbi.nlm.nih.gov/pubmed/20502317.
16. Lundberg BE, Davidson AJ, Burman WJ. Epidemiology of Pneumocystis carinii pneumonia in an era of effective prophylaxis: the relative contribution of non-adherence and drug failure. *AIDS*. Nov 10 2000;14(16):2559-2566. Available at http://www.ncbi.nlm.nih.gov/pubmed/11101068.
17. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest*. Dec 2001;120(6):1888-1893. Available at http://www.ncbi.nlm.nih.gov/pubmed/11742918.
18. Kovacs JA, Hiemenz JW, Macher AM, et al. Pneumocystis carinii pneumonia: a comparison between patients

with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med*. May 1984;100(5):663-671. Available at http://www.ncbi.nlm.nih.gov/pubmed/6231873.

19. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of Pneumocystis carinii pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. May 28 1998;12(8):885-893. Available at http://www.ncbi.nlm.nih.gov/pubmed/9631142.
20. Ng VL, Yajko DM, Hadley WK. Extrapulmonary pneumocystosis. *Clin Microbiol Rev*. Jul 1997;10(3):401-418. Available at http://www.ncbi.nlm.nih.gov/pubmed/9227859.
21. Smith DE, McLuckie A, Wyatt J, Gazzard B. Severe exercise hypoxaemia with normal or near normal X-rays: a feature of Pneumocystis carinii infection. *Lancet*. Nov 5 1988;2(8619):1049-1051. Available at http://www.ncbi.nlm.nih.gov/pubmed/2903279.
22. Zaman MK, White DA. Serum lactate dehydrogenase levels and Pneumocystis carinii pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis*. Apr 1988;137(4):796-800. Available at http://www.ncbi.nlm.nih.gov/pubmed/3258483.
23. Opravil M, Marincek B, Fuchs WA, et al. Shortcomings of chest radiography in detecting Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr*. Jan 1994;7(1):39-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/8263751.
24. Metersky ML, Colt HG, Olson LK, Shanks TG. AIDS-related spontaneous pneumothorax. Risk factors and treatment. *Chest*. Oct 1995;108(4):946-951. Available at http://www.ncbi.nlm.nih.gov/pubmed/7555166.
25. Sepkowitz KA, Telzak EE, Gold JW, et al. Pneumothorax in AIDS. *Ann Intern Med*. Mar 15 1991;114(6):455-459. Available at http://www.ncbi.nlm.nih.gov/pubmed/1994791.
26. Baughman RP, Dohn MN, Frame PT. The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients. *Am J Med*. Dec 1994;97(6):515-522. Available at http://www.ncbi.nlm.nih.gov/pubmed/7985710.
27. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med*. Jul 1984;101(1):1-7. Available at http://www.ncbi.nlm.nih.gov/pubmed/6375497.
28. Gruden JF, Huang L, Turner J, et al. High-resolution CT in the evaluation of clinically suspected Pneumocystis carinii pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. *AJR Am J Roentgenol*. Oct 1997;169(4):967-975. Available at http://www.ncbi.nlm.nih.gov/pubmed/9308446.
29. Hidalgo A, Falco V, Mauleon S, al. e. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non-Pneumocystis carinii pneumonia in AIDS Patients. *European Radiology*. 2003;13:1179-1184.
30. Roger PM, Vandenbos F, Pugliese P, et al. Persistence of Pneumocystis carinii after effective treatment of P. carinii pneumonia is not related to relapse or survival among patients infected with human immunodeficiency virus. *Clin Infect Dis*. Feb 1998;26(2):509-510. Available at http://www.ncbi.nlm.nih.gov/pubmed/9502487.
31. Harris JR, Marston BJ, Sangrujee N, DuPlessis D, Park B. Cost-effectiveness analysis of diagnostic options for pneumocystis pneumonia (PCP). *PLoS One*. 2011;6(8):e23158. Available at http://www.ncbi.nlm.nih.gov/pubmed/21858013.
32. Torres J, Goldman M, Wheat LJ, et al. Diagnosis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients with polymerase chain reaction: a blinded comparison to standard methods. *Clin Infect Dis*. Jan 2000;30(1):141-145. Available at http://www.ncbi.nlm.nih.gov/pubmed/10619742.
33. Larsen HH, Masur H, Kovacs JA, et al. Development and evaluation of a quantitative, touch-down, real-time PCR assay for diagnosing Pneumocystis carinii pneumonia. *J Clin Microbiol*. Feb 2002;40(2):490-494. Available at http://www.ncbi.nlm.nih.gov/pubmed/11825961.
34. Larsen HH, Huang L, Kovacs JA, et al. A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of Pneumocystis pneumonia in HIV-infected patients. *J Infect Dis*. May 1 2004;189(9):1679-1683. Available at http://www.ncbi.nlm.nih.gov/pubmed/15116305.
35. Pisculli ML, Sax PE. Use of a serum beta-glucan assay for diagnosis of HIV-related Pneumocystis jiroveci pneumonia in patients with negative microscopic examination results. *Clin Infect Dis*. Jun 15 2008;46(12):1928-1930. Available at http://www.ncbi.nlm.nih.gov/pubmed/18540807.

36. Sax PE, Komarow L, Finkelman MA, et al. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related Pneumocystis jirovecii pneumonia. *Clin Infect Dis*. Jul 15 2011;53(2):197-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/21690628.

37. Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of Pneumocystis jirovecii in the surrounding air of patients with Pneumocystis pneumonia. *Clin Infect Dis*. Aug 1 2010;51(3):259-265. Available at http://www.ncbi.nlm.nih.gov/pubmed/20572759.

38. Pliquett RU, Asbe-Vollkopf A, Hauser PM, et al. A Pneumocystis jirovecii pneumonia outbreak in a single kidney-transplant center: role of cytomegalovirus co-infection. Eur *J Clin Microbiol* Infect Dis. Sep 2012;31(9):2429-2437. Available at http://www.ncbi.nlm.nih.gov/pubmed/22402816.

39. Centers for Disease Controm and Prevention. Guidelines for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. Jun 16 1989;38 Suppl 5(Suppl 5):1-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/2524643.

40. Heald A, Flepp M, Chave JP, et al. Treatment for cerebral toxoplasmosis protects against Pneumocystis carinii pneumonia in patients with AIDS. The Swiss HIV Cohort Study. *Ann Intern Med*. Nov 15 1991;115(10):760-763. Available at http://www.ncbi.nlm.nih.gov/pubmed/1929023.

41. Bozzette SA, Finkelstein DM, Spector SA, et al; with the NIAID AIDS Clinical Trials Group. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med*. Mar 16 1995;332(11):693-699. Available at http://www.ncbi.nlm.nih.gov/pubmed/7854375.

42. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al; with the The Dutch AIDS Treatment Group. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med*. Dec 24 1992;327(26):1836-1841. Available at http://www.ncbi.nlm.nih.gov/pubmed/1360145.

43. Schneider MM, Nielsen TL, Nelsing S, et al; with Dutch AIDS Treatment Group. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus. *J Infect Dis*. Jun 1995;171(6):1632-1636. Available at http://www.ncbi.nlm.nih.gov/pubmed/7769306.

44. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al; with Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis*. Oct 1999;29(4):775-783. Available at http://www.ncbi.nlm.nih.gov/pubmed/10589887.

45. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. Jul 15 1992;117(2):106-111. Available at http://www.ncbi.nlm.nih.gov/pubmed/1351371.

46. Hardy WD, Feinberg J, Finkelstein DM, et al; with AIDS Clinical Trials Group Protocol 021. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Dec 24 1992;327(26):1842-1848. Available at http://www.ncbi.nlm.nih.gov/pubmed/1448121.

47. Para MF, Finkelstein D, Becker S, Dohn M, Walawander A, Black JR. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr*. Aug 1 2000;24(4):337-343. Available at http://www.ncbi.nlm.nih.gov/pubmed/11015150.

48. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. Oct 15 2001;184(8):992-997. Available at http://www.ncbi.nlm.nih.gov/pubmed/11574913.

49. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. May 15 1995;122(10):755-761. Available at http://www.ncbi.nlm.nih.gov/pubmed/7717598.

50. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human

immunodeficiency virus-infected patients. *Clin Infect Dis*. Mar 1995;20(3):531-541. Available at http://www.ncbi.nlm.nih.gov/pubmed/7756472.

51. Girard PM, Landman R, Gaudebout C, al. e. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt= AbstractPlus&list_uids=8479488&query_hl= 14&itool=pubmed_docsum.
52. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis*. Aug 1999;180(2):369-376. Available at http://www.ncbi.nlm.nih.gov/pubmed/10395851.
53. El-Sadr WM, Murphy RL, Yurik TM, et al; with Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med*. Dec 24 1998;339(26):1889-1895. Available at http://www.ncbi.nlm.nih.gov/pubmed/9862944.
54. Payen MC, De Wit S, Sommereijns B, Clumeck N. A controlled trial of dapsone versus pyrimethamine-sulfadoxine for primary prophylaxis of Pneumocystis carinii pneumonia and toxoplasmosis in patients with AIDS. *Biomed Pharmacother*. 1997;51(10):439-445. Available at http://www.ncbi.nlm.nih.gov/pubmed/9863502.
55. Schurmann D, Bergmann F, Albrecht H, et al. Twice-weekly pyrimethamine-sulfadoxine effectively prevents Pneumocystis carinii pneumonia relapse and toxoplasmic encephalitis in patients with AIDS. *J Infect*. Jan 2001;42(1):8-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/11243747.
56. Schurmann D, Bergmann F, Albrecht H, et al. Effectiveness of twice-weekly pyrimethamine-sulfadoxine as primary prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis in patients with advanced HIV infection. Eur *J Clin Microbiol* Infect Dis. May 2002;21(5):353-361. Available at http://www.ncbi.nlm.nih.gov/pubmed/12072919.
57. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for Pneumocystis carinii infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/2860516.
58. Furrer H, Egger M, Opravil M, et al; Swiss HIV Cohort Study. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. *N Engl J Med*. Apr 29 1999;340(17):1301-1306. Available at http://www.ncbi.nlm.nih.gov/pubmed/10219064.
59. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/10915098.
60. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. May 2000;181(5):1635-1642. Available at http://www.ncbi.nlm.nih.gov/pubmed/10823763.
61. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for Pneumocystis carinii pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. Jan 16 1999;353(9148):201-203. Available at http://www.ncbi.nlm.nih.gov/pubmed/9923876.
62. Weverling GJ, Mocroft A, Ledergerber B, et al; with the EuroSIDA Study Group. Discontinuation of Pneumocystis carinii pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. *Lancet*. Apr 17 1999;353(9161):1293-1298. Available at http://www.ncbi.nlm.nih.gov/pubmed/10218526.
63. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD; with the HIV Outpatient Study (HOPS) Investigators. Discontinuation of chemoprophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection. *Ann Intern Med*. Feb 1 2000;132(3):201-205. Available at http://www.ncbi.nlm.nih.gov/pubmed/10651600.
64. Furrer H, Opravil M, Rossi M, et al. Discontinuation of primary prophylaxis in HIV-infected patients at high risk of Pneumocystis carinii pneumonia: prospective multicentre study. *AIDS*. Mar 9 2001;15(4):501-507. Available at http://www.ncbi.nlm.nih.gov/pubmed/11242147.
65. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. Sep 10 1999;13(13):1647-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/10509565.
66. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al; with the Grupo de Estudio del SIDA 04/98. A randomized trial

of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. *N Engl J Med*. Jan 18 2001;344(3):159-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/11172138.

67. Green H, Hay P, Dunn DT, McCormack S, Investigators S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. *HIV Med*. Jul 2004;5(4):278-283. Available at http://www.ncbi.nlm.nih.gov/pubmed/15236617.
68. Opportunistic Infections Project Team of the Collaboration of Observational HIVERiE, Mocroft A, Reiss P, et al. Is it safe to discontinue primary Pneumocystis jiroveci pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. Sep 1 2010;51(5):611-619. Available at http://www.ncbi.nlm.nih.gov/pubmed/20645862.
69. D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA, Angel JB. Pneumocystis jiroveci pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/microl when viral replication is suppressed. *AIDS*. Aug 20 2007;21(13):1711-1715. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690568.
70. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med*. May 27 1993;328(21):1521-1527. Available at http://www.ncbi.nlm.nih.gov/pubmed/8479489.
71. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. May 1 1996;124(9):792-802. Available at http://www.ncbi.nlm.nih.gov/pubmed/8610948.
72. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis*. Oct 1994;170(4):912-917. Available at http://www.ncbi.nlm.nih.gov/pubmed/7930736.
73. Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated Pneumocystis pneumonia containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. *AIDS*. May 20 2005;19(8):801-805. Available at http://www.ncbi.nlm.nih.gov/pubmed/15867494.
74. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in Pneumocystis and sulfa resistance. *Emerg Infect Dis*. Oct 2004;10(10):1721-1728. Available at http://www.ncbi.nlm.nih.gov/pubmed/15504256.
75. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and Pneumocystis jirovecii pneumonia. *Emerg Infect Dis*. Oct 2004;10(10):1760-1765. Available at http://www.ncbi.nlm.nih.gov/pubmed/15504261.
76. Alvarez-Martinez MJ, Miro JM, Valls ME, et al. Prevalence of dihydropteroate synthase genotypes before and after the introduction of combined antiretroviral therapy and their influence on the outcome of Pneumocystis pneumonia in HIV-1-infected patients. *Diagn Microbiol Infect Dis*. Sep 2010;68(1):60-65. Available at http://www.ncbi.nlm.nih.gov/pubmed/20727472.
77. Nielsen TL, Eeftinck Schattenkerk JK, Jensen BN, et al. Adjunctive corticosteroid therapy for Pneumocystis carinii pneumonia in AIDS: a randomized European multicenter open label study. *J Acquir Immune Defic Syndr*. 1992;5(7):726-731. Available at http://www.ncbi.nlm.nih.gov/pubmed/1613673.
78. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. Nov 22 1990;323(21):1451-1457. Available at http://www.ncbi.nlm.nih.gov/pubmed/2233917.
79. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med*. Nov 22 1990;323(21):1500-1504. Available at http://www.ncbi.nlm.nih.gov/pubmed/2136587.
80. Montaner JS, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe Pneumocystis carinii pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med*. Jul 1 1990;113(1):14-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/2190515.
81. Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of Pneumocystis carinii pneumonia on mortality and subsequent complications. *Chest*. Nov 1998;114(5):1258-1263. Available at http://www.

ncbi.nlm.nih.gov/pubmed/9823998.

82. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection. *Cochrane Database Syst Rev*. 2006;3:CD006150(3):CD006150. Available at http://www.ncbi.nlm.nih.gov/pubmed/16856118.
83. Medina I, Mills J, Leoung G, et al. Oral therapy for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med*. Sep 20 1990;323(12):776-782. Available at http://www.ncbi.nlm.nih.gov/pubmed/2392131.
84. Black JR, Feinberg J, Murphy RL, et al. Clindamycin and primaquine therapy for mild-to-moderate episodes of Pneumocystis carinii pneumonia in patients with AIDS: AIDS Clinical Trials Group 044. *Clin Infect Dis*. Jun 1994;18(6):905-913. Available at http://www.ncbi.nlm.nih.gov/pubmed/8086551.
85. Toma E, Thorne A, Singer J, et al; with the CTN-PCP Study Group. Clindamycin with primaquine vs. Trimethoprim-sulfamethoxazole therapy for mild and moderately severe Pneumocystis carinii pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). *Clin Infect Dis*. Sep 1998;27(3):524-530. Available at http://www.ncbi.nlm.nih.gov/pubmed/9770152.
86. Smego RA, Jr., Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med*. Jun 25 2001;161(12):1529-1533. Available at http://www.ncbi.nlm.nih.gov/pubmed/11427101.
87. Dohn MN, Weinberg WG, Torres RA, et al; with the Atovaquone Study Group. Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. *Ann Intern Med*. Aug 1 1994;121(3):174-180. Available at http://www.ncbi.nlm.nih.gov/pubmed/7880228.
88. Conte JE, Jr., Chernoff D, Feigal DW, Jr., Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating Pneumocystis carinii pneumonia in AIDS. A randomized trial. *Ann Intern Med*. Aug 1 1990;113(3):203-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/2197911.
89. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. *Ann Intern Med*. Jul 1986;105(1):37-44. Available at http://www.ncbi.nlm.nih.gov/pubmed/3521428.
90. Kim T, Kim SH, Park KH, et al. Clindamycin-primaquine versus pentamidine for the second-line treatment of pneumocystis pneumonia. *J Infect Chemother*. Oct 2009;15(5):343-346. Available at http://www.ncbi.nlm.nih.gov/pubmed/19856077.
91. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated Pneumocystis jirovecii pneumonia: a tri-centre cohort study. *J Antimicrob Chemother*. Dec 2009;64(6):1282-1290. Available at http://www.ncbi.nlm.nih.gov/pubmed/19858161.
92. Benfield T, Atzori C, Miller RF, Helweg-Larsen J. Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr*. May 1 2008;48(1):63-67. Available at http://www.ncbi.nlm.nih.gov/pubmed/18360286.
93. Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for Pneumocystis carinii pneumonia in AIDS. A randomized trial. *Ann Intern Med*. Aug 1 1990;113(3):195-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/2197910.
94. Montgomery AB, Feigal DW, Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for Pneumocystis carinii in acquired immune deficiency syndrome. *Am J Respir Crit Care Med*. Apr 1995;151(4):1068-1074. Available at http://www.ncbi.nlm.nih.gov/pubmed/7697233.
95. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of Pneumocystis carinii pneumonia, in the United States. *J Infect Dis*. May 1 2001;183(9):1409-1412. Available at http://www.ncbi.nlm.nih.gov/pubmed/11294675.
96. Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe Pneumocystis carinii pneumonia. *AIDS*. Jan 3 2003;17(1):73-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/12478071.
97. Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe Pneumocystis jirovecii pneumonia is independent of highly active antiretroviral therapy. *Thorax*. Aug 2006;61(8):716-721. Available at http://www.ncbi.nlm.nih.gov/pubmed/16601092.
98. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients With HIV admitted to the ICU

continues to improve in the current era of combination antiretroviral therapy. *Chest*. Jan 2009;135(1):11-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/18719058.

99. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/pubmed/19440326.
100. Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PLoS One*. 2010;5(7):e11416. Available at http://www.ncbi.nlm.nih.gov/pubmed/20617176.
101. Jagannathan P, Davis E, Jacobson M, Huang L. Life-threatening immune reconstitution inflammatory syndrome after Pneumocystis pneumonia: a cautionary case series. *AIDS*. Aug 24 2009;23(13):1794-1796. Available at http://www.ncbi.nlm.nih.gov/pubmed/19684486.
102. Eeftinck Schattenkerk JK, Lange JM, van Steenwijk RP, Danner SA. Can the course of high dose cotrimoxazole for Pneumocystis carinii pneumonia in AIDS be shorter? A possible solution to the problem of cotrimoxazole toxicity. *J Intern Med*. May 1990;227(5):359-362. Available at http://www.ncbi.nlm.nih.gov/pubmed/2341830.
103. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. Apr 1984;100(4):495-499. Available at http://www.ncbi.nlm.nih.gov/pubmed/6230976.
104. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related Pneumocystis carinii pneumonia. *J Infect Dis*. May 1995;171(5):1295-1301. Available at http://www.ncbi.nlm.nih.gov/pubmed/7751706.
105. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for Pneumocystis carinii pneumonia in AIDS patients: results of a large prospective randomized treatment trial. *AIDS*. Mar 1992;6(3):301-305. Available at http://www.ncbi.nlm.nih.gov/pubmed/1567574.
106. Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of Pneumocystis carinii pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. *J Infect Dis*. Jul 1994;170(1):165-172. Available at http://www.ncbi.nlm.nih.gov/pubmed/8014493.
107. Masur H, Kaplan JE, Holmes KK, Service USPH, Infectious Diseases Society of A. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med*. Sep 3 2002;137(5 Pt 2):435-478. Available at http://www.ncbi.nlm.nih.gov/pubmed/12617574.
108. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Mar 10 2000;14(4):383-386. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770540.
109. Zellweger C, Opravil M, Bernasconi E, et al. Long-term safety of discontinuation of secondary prophylaxis against Pneumocystis pneumonia: prospective multicentre study. *AIDS*. Oct 21 2004;18(15):2047-2053. Available at http://www.ncbi.nlm.nih.gov/pubmed/15577626.
110. Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients: a randomized trial by the CIOP Study Group. *Clin Infect Dis*. Mar 1 2003;36(5):645-651. Available at http://www.ncbi.nlm.nih.gov/pubmed/12594647.
111. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. Jan 18 2001;344(3):168-174. Available at http://www.ncbi.nlm.nih.gov/pubmed/11188837.
112. Ahmad H, Mehta NJ, Manikal VM, et al. Pneumocystis carinii pneumonia in pregnancy. *Chest*. Aug 2001;120(2):666-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11502676.
113. Connelly RT, Lourwood DL. Pneumocystis carinii pneumonia prophylaxis during pregnancy. *Pharmacotherapy*. Jul–Aug 1994;14(4):424-429. Available at http://www.ncbi.nlm.nih.gov/pubmed/7937279.
114. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at http://www.ncbi.nlm.nih.gov/

pubmed/11738517.

115. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at http://www.ncbi.nlm.nih.gov/pubmed/11096168.
116. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *American Journal of Epidemiology*. May 15 2001;153(10):961-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/11384952.
117. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sexually Transmitted Infections*. Dec 2001;77(6):441-443. Available at http://www.ncbi.nlm.nih.gov/pubmed/11714944.
118. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep*. Sep 11 1992;41(RR-14):1-7. Available at http://www.ncbi.nlm.nih.gov/pubmed/1522835.
119. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reproductive Toxicology*. Nov–Dec 2001;15(6):637-646. Available at http://www.ncbi.nlm.nih.gov/pubmed/11738517.
120. Razavi B, Lund B, Allen BL, Schlesinger L. Failure of trimethoprim/sulfamethoxazole prophylaxis for Pneumocystis carinii pneumonia with concurrent leucovorin use. *Infection*. Jan 2002;30(1):41-42. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11876516.
121. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. Oct 1956;18(4):614-625. Available at http://www.ncbi.nlm.nih.gov/pubmed/13370229.
122. Albino JA, Shapiro JM. Respiratory failure in pregnancy due to Pneumocystis carinii: report of a successful outcome. *Obstet Gynecol*. May 1994;83(5 Pt 2):823-824. Available at http://www.ncbi.nlm.nih.gov/pubmed/8159362.
123. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? *Am J Obstet Gynecol*. Sep 1989;161(3):657-662. Available at http://www.ncbi.nlm.nih.gov/pubmed/2782348.
124. Koonin LM, Ellerbrock TV, Atrash HK, et al. Pregnancy-associated deaths due to AIDS in the United States. *JAMA*. Mar 3 1989;261(9):1306-1309. Available at http://www.ncbi.nlm.nih.gov/pubmed/2783746.
125. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. *Am J Obstet Gynecol*. Oct 15 1982;144(4):413-417. Available at http://www.ncbi.nlm.nih.gov/pubmed/7124859.
126. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. Dec 2000;62(6):385-392. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11091360.
127. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology*. Nov 1997;56(5):335-340. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9451758.
128. Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J*. Nov 2003;40(6):624-628. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14577813.
129. Ostensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16712713.
130. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. Jul-Aug 1986;11(4):299-315. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3530584.
131. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15230645.
132. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-

Saharan Africa. *Trop Med Int Health*. Jun 2003;8(6):488-506. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12791054.

133. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. May 1989;82(5):668. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2717998.

134. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. Jan 2006;1(1):1-15. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18690910.

135. Harstad TW, Little BB, Bawdon RE, Knoll K, Roe D, Gilstrap LC, 3rd. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. *Am J Obstet Gynecol*. Sep 1990;163(3):912-916. Available at http://www.ncbi.nlm.nih.gov/pubmed/2403167.

Toxoplasma gondii Encephalitis (Last updated December 10, 2015; last reviewed June 14, 2017)

NOTE: Update in Progress

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts.[1-4] Primary infection occasionally is associated with acute cerebral or disseminated disease.

Epidemiology

Seroprevalence of anti-*Toxoplasma* antibody varies substantially among different geographic locales, with a prevalence of approximately 11% in the United States, versus 50% to 80% in certain European, Latin American, and African countries.[4-6] In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunosuppression who were seropositive for *T. gondii* and not receiving prophylaxis with drugs against the disease. A low incidence of toxoplasmosis is seen in patients who are seronegative for *T. gondii*. If patients are truly seronegative, their toxoplasmosis presumably represents one of three possible scenarios:

1) Primary infection,
2) Re-activation of latent disease in individuals who cannot produce detectable antibodies, *or*
3) Testing with insensitive assays.[7,8]

Clinical disease is rare among patients with CD4 T lymphocyte (CD4) cell counts >200 cells/μL. Patients with CD4 counts <50 cells/μL are at greatest risk.[1,3,8,9] Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In the United States, eating raw shellfish including oysters, clams, and mussels recently was identified as a novel risk factor for acute infection.[10] Up to 50% of individuals with documented primary infection do not have an identifiable risk factor.[11] The organism is not transmitted through person-to-person contact.

Clinical Manifestations

Among patients with AIDS, the most common clinical presentation of *T. gondii* infection is focal encephalitis with headache, confusion, or motor weakness and fever.[1,3,9] Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms. Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement are rare in patients with AIDS. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will typically show multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema.[1,9,12-14] Toxoplasmosis also can manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.[15] This latter presentation tends to be rapidly progressive and fatal.

Diagnosis

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.[1,3,9,16] The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies usually are absent. Quantitative antibody titers are not useful for diagnosis.

Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. On imaging studies, lesions are usually ring-enhancing and have a predilection for the basal ganglia. MRI has sensitivity

superior to that of CT studies for radiological diagnosis of TE. Positron emission tomography[13] or single-photon emission computed tomography scanning[14] may be helpful in distinguishing between TE and primary central nervous system (CNS) lymphoma, but no imaging technique is completely specific. For TE, detection of the organism requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Hematoxylin and eosin stains can be used for detection of *T. gondii*, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.[17] If safe and feasible, a lumbar puncture should be performed for *T. gondii* polymerase chain reaction (PCR), as well as for cytology, culture, cryptococcal antigen and PCR for *Mycobacterium tuberculosis*, Epstein-Barr Virus (EBV) and JC Virus (JCV), either at initial presentation or subsequently, especially in patients in whom empiric therapy fails. Detection of *T. gondii* by PCR in cerebrospinal fluid (CSF) has high specificity (96% to 100%), but low sensitivity (50%), especially once specific anti-toxoplasma therapy has been started.[18-20]

The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leucoencephalopathy (PML). In the absence of immune reconstitution inflammatory syndrome (IRIS), PML (but not lymphoma) can be distinguished on the basis of imaging studies. PML lesions typically involve white matter rather than gray matter, are non-contrast enhancing, and produce no mass effect. Less common causes of focal neurologic disease in patients with AIDS include mycobacterial infection (especially tuberculosis [TB]); fungal infection, such as cryptococcosis; Chagas disease; and pyogenic brain abscess, particularly in IV drug abusers.

Most clinicians initially rely on an empiric diagnosis, which can be established as an objective response, documented by clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis. Brain biopsy is reserved for patients who fail to respond to specific therapy, although earlier biopsy should be strongly considered if results from imaging, serology, or PCR suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing mass lesions, detection of EBV and JCV by PCR in CSF is highly suggestive of CNS lymphoma[21,22] or PML,[23] respectively.

Preventing Exposure

HIV-infected individuals should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (BIII). They also should be counseled regarding sources of *Toxoplasma* infection, especially if they lack IgG antibody to *Toxoplasma*.

To minimize risk of acquiring toxoplasmosis, HIV-infected individuals should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison, and not to eat raw shellfish including oysters, clams, and mussels **(BIII)**. Lamb, beef, venison, and pork should be cooked to an internal temperature of 165°F to 170°F;[24] meat cooked until it is no longer pink inside usually has an internal temperature of 165°F to 170°F, and therefore, from a more practical perspective, satisfies this requirement. To minimize the risk for acquiring toxoplasmosis, HIV-infected individuals should wash their hands after contact with raw meat and after gardening or other contact with soil; they should also wash fruits and vegetables well before eating them raw **(BIII)**. Patients who are seronegative and who own cats should be advised to have someone who is HIV-negative and not pregnant change the litter box daily. If they must change the litter box themselves, they should wash their hands thoroughly after doing so **(BIII)**. HIV-infected patients also should be encouraged to keep their cats inside and not to adopt or handle stray cats **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis **(AII)**.

Preventing Disease

Indication for Primary Prophylaxis

Toxoplasma-seropositive patients who have CD4 counts <100 cells/µL should receive prophylaxis against TE **(AII)**.[25,26]

The double-strength-tablet daily dose of trimethoprim-sulfamethoxazole (TMP-SMX), which is the preferred regimen for *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, is effective against TE and is recommended **(AII)**. TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BIII)**. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP **(BI)**.[27-29] Atovaquone with or without pyrimethamine/leucovorin is active against PCP and also can be considered **(CIII)**. Aerosolized pentamidine does not protect against TE and **is not recommended** for antitoxoplasma prophylaxis **(AI)**.[25,30]

Toxoplasma-seronegative persons who are not taking a PCP prophylactic regimen known to be active against TE, such as aerosolized pentamidine, should be retested for IgG antibody to *Toxoplasma* when their CD4 counts decline to <100 cells/µL to determine whether they have seroconverted and therefore are at risk for TE. Patients who have seroconverted should be administered prophylaxis for TE as previously described **(AII)**.

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued in adult and adolescent patients receiving ART whose CD4 counts increase to >200 cells/µL for more than 3 months **(AI)**. Multiple observational studies[31-33] and two randomized trials[34,35] have reported that primary prophylaxis can be discontinued, with minimal risk for development of TE, in patients receiving ART whose CD4 counts increase from <200 cells/µL to >200 cells/µL for more than 3 months. In these studies, most patients were taking HIV protease inhibitor-containing regimens and the median CD4 count at the time prophylaxis was discontinued was >300 cells/µL. At the time prophylaxis was discontinued, most patients had sustained suppression of plasma HIV RNA levels below the detection limits of available assays; the median follow-up was 7 to 22 months. Patients with CD4 counts of <100 cells/µL are at greatest risk for having TE, but the risk for TE with CD4 counts of 100 to 200 cells/µL has not been studied as rigorously as increases to >200 cells/µL. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/µL. When CD4 counts are >200 cells/µL for at least 3 months, primary TE prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, likelihood of development of drug-resistant pathogens, and cost. Prophylaxis for TE should be reintroduced if the CD4 count decreases to <100 to 200 cells/µL **(AIII)**. When a decision to stop PCP prophylaxis is contemplated in patients with CD4 counts of 100 to 200 cells/µL and plasma HIV RNA viral loads below the limits of detection with commercial assays, toxoplasma serostatus should be considered, because seropositive patients may then be at risk for developing TE.

Treating Disease

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI)**.[2,36-38] Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.[39] Leucovorin reduces the likelihood of development of hematologic toxicities associated with pyrimethamine therapy.[40] Pyrimethamine plus clindamycin plus leucovorin **(AI)**[36,37] is the preferred alternative regimen for patients with TE who cannot tolerate sulfadiazine or do not respond to first-line therapy. This combination, however, does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used **(AII)** (see discussion under Preventing Recurrence).

In a small (77 patients), randomized trial, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.[41] Others have reported similar efficacy in open-label observational studies.[42] TMP-SMX has less in vitro activity and experience using this drug to treat toxoplasmosis in developed countries is limited. However, if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin **(BI)**. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies **(BI)**.[43-48] Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved **(CIII)**.

No well-studied options exist for patients who cannot take an oral regimen. No parenteral formulation of pyrimethamine exists and the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Some specialists will use parenteral TMP-SMX **(BI)** or oral pyrimethamine plus

parenteral clindamycin **(CIII)** as initial treatment in severely ill patients who require parenteral therapy.

The following regimens have been shown to be effective in treating TE in at least two nonrandomized, uncontrolled trials, although their relative efficacy compared with the previous regimens is unknown: atovaquone (with meals or oral nutritional supplements) plus either pyrimethamine plus leucovorin or sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent **(BII)**[49,50,51] (if atovaquone is used alone, clinicians should be aware that the absorption of the drug from patient to patient is highly variable; plasma levels >18.5 µg/mL are associated with an improved response rate but measurements are not routinely available);[50-52] and azithromycin plus pyrimethamine plus leucovorin daily **(CII)**.[53,54]

The following regimens have been reported to have activity in treatment of TE in small cohorts of patients or in case reports of one or several patients: clarithromycin plus pyrimethamine **(CIII)**;[55] 5-fluorouracil plus clindamycin **(CIII)**,[56] dapsone plus pyrimethamine plus leucovorin **(CIII)**;[57] and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin **(CIII)**.[58,59] Although the clarithromycin dose used in the only published study was 1g twice a day, doses >500 mg have been associated with increased mortality in HIV-infected patients treated for disseminated *Mycobacterium avium* complex. Doses >500 mg twice a day **should not be used (BIII)**.

Clinical response to acute therapy occurs in 90% of patients with TE within 14 days of initiation of appropriate anti-toxoplasma treatment.[2] The reasons why some patients fail therapy are not clearly proven; whether such failures are due to poor adherence or to other host factors of antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement **(BII)**.[1-4] Longer courses may be appropriate if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below (see Preventing Recurrence section below). The radiologic goals for treatment include complete resolution of the lesion(s) in terms of size and contrast enhancement, although small scars may persist indefinitely. Adjunctive corticosteroids such as dexamethasone should only be administered to patients with TE when they are clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII)**. In those treated with corticosteroids, caution may be needed in diagnosing CNS toxoplasmosis on the basis of treatment response, since primary CNS lymphoma may respond clinically and radiographically to corticosteroids alone; these patients should be monitored carefully as corticosteroids are tapered. In addition, corticosteroids should be discontinued as soon as clinically feasible because of their potential to cause immunosuppression. Patients receiving corticosteroids should be monitored closely for development of other opportunistic infections (OIs), including cytomegalovirus retinitis and TB.

Anticonvulsants should be administered to patients with TE who have a history of seizures **(AIII)**, but **should not be administered** prophylactically to all patients **(BIII)**. Anticonvulsants, if administered, should be continued at least through the period of acute therapy.

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no data on which to base a recommendation regarding when to start ART in a patient with TE. However, many physicians would initiate ART within 2 to 3 weeks after the diagnosis of toxoplasmosis **(CIII)**, based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the ART arm of a controlled trial of 282 patients with OIs other than TB (only 5% of whom had toxoplasmosis) who were randomized to early (median 12 days after initiation of OI therapy) versus deferred (median 45 days) initiation of ART.[60]

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement **(AIII)**. Common pyrimethamine toxicities such as rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) often can be reversed by increasing the leucovorin dose to 10, 25, or 50 mg, four times daily **(CIII)**.

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including

pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Common atovaquone toxicities include nausea, vomiting, diarrhea, rash, headache, hyperglycemia, and fever. Drug interactions between anticonvulsants and antiretroviral agents should be evaluated carefully; if necessary, doses should be adjusted or alternative anticonvulsants should be used.

IRIS associated with TE has been reported but appears to be rare (~5% in one report).[61-63] Given the rarity of TE-associated IRIS, recommendations for management of such events are difficult to develop.

Managing Treatment Failure

A brain biopsy should be strongly considered in patients who did not have an initial biopsy prior to therapy and who fail to respond to initial therapy for TE **(BII)** as defined by clinical or radiologic deterioration during the first week despite adequate therapy, or who do not show clinical improvement within 10 to 14 days. A switch to an alternative regimen, as previously described, should be considered for those who undergo brain biopsy and have confirmed histopathologic evidence of TE, or who have a CSF PCR positive for *T. gondii* **(BIII)**. In patients who adhere to their regimens, disease recurrence is unusual in the setting of chronic maintenance therapy after an initial clinical and radiographic response.

Preventing Recurrence

When to Start Chronic Maintenance Therapy

Patients who have completed initial therapy for TE should be given chronic maintenance therapy to suppress infection **(AI)**[36,37] until immune reconstitution occurs as a consequence of ART, in which case treatment discontinuation is indicated. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE **(AI)** and provides protection against PCP **(AII)**. Although sulfadiazine is routinely dosed as a four-times-a-day regimen, a pharmacokinetic study suggests bioequivalence for the same total daily dose when given either twice or four times a day,[64] and limited clinical experience suggests that twice-daily dosing is effective.[65] Pyrimethamine plus clindamycin is commonly used as suppressive therapy for patients with TE who cannot tolerate sulfa drugs **(BI)**. Because of the high failure rate observed with lower doses,[36] a dose of 600 mg clindamycin every 8 hours is recommended **(CIII)**. Because this regimen does not provide protection against PCP **(AII)**, an additional agent, such as aerosol pentamidine, must be used. Atovaquone with or without pyrimethamine or sulfadiazine is also active against both TE[51,52] and PCP[66] **(BII)**, but is substantially more expensive. A small, uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen to reduce pill burden.[67] For patients being treated with TMP-SMX, this drug should be continued as chronic maintenance, at a reduced dose of 1 double-strength tablet twice daily **(BII)** or once daily **(BII)**. The lower dose may be associated with an increased risk of relapse, and if the once daily dosing is used, a gradual transition may be beneficial (e.g. follow acute therapy with 4–6 weeks of 1 double-strength tablet twice daily before lowering to 1 double-strength tablet once daily **(CIII)**.[41,42,68]

Although there are no data on the long-term suppressive efficacy of the other alternative regimens noted above, clinicians might consider using these agents in unusual situations in which the recommended agents cannot be administered **(CIII)**.

When to Stop Chronic Maintenance Therappy

Adult and adolescent patients receiving chronic maintenance therapy for TE are at low risk for recurrence of TE if they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increase in their CD4 counts to >200 cells/μL after ART that is sustained for more than 6 months.[32,35,69,70] Discontinuing chronic maintenance therapy in such patients is a reasonable consideration, although occasional recurrences have been reported. The recommendation is based on results in a limited number of patients from observational studies and one randomized clinical trial and inference from more extensive cumulative data indicating the safety of discontinuing secondary prophylaxis for other

OIs during advanced disease **(BI)**. As part of the evaluation to determine whether discontinuation of therapy is appropriate, some specialists recommend obtaining an MRI of the brain to assess for resolution of brain lesions.

Secondary prophylaxis (chronic maintenance therapy) for TE should be reintroduced if the CD4 count decreases to <200 cells/μL **(AIII)**.

Special Considerations During Pregnancy

Documentation of baseline maternal *T. gondii* serologic status (IgG) should be obtained in HIV-infected women who are pregnant. Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, IgA, and IgE antibodies; IgG avidity; and the differential agglutination tests.[71,72] Pregnant HIV-infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist or another appropriate specialist who can perform specialized laboratory testing **(BIII)**[72,73] (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory; Palo Alto, CA; http://www.pamf.org/serology/ at 650-853-4828 and toxolab@pamf.org; and the National Collaborative Chicago-based Congenital Toxoplasmosis Study; Chicago, IL; http://www.uchospitals.edu/specialties/infectious-diseases/toxoplasmosis/ at 773-834-4131 and rmcleod@midway.uchicago.edu).

Toxoplasmosis diagnostic considerations are the same in pregnant women as in non-pregnant women.

Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or suspected symptomatic disease in the mother and the risk of transmission of the parasite from mother to fetus. Maternal treatment of TE should be the same as in non-pregnant adults **(BIII)**, including pyrimethamine plus sulfadiazine plus leucovorin **(AI)**.[2,36-38] This regimen is also believed to prevent mother-to-child transmission of *T. gondii* and it may be therapeutic for affected fetuses.[72]

Although pyrimethamine has been associated with birth defects in animals, human data have not suggested an increased risk for defects, therefore, it can be administered to pregnant women after the first trimester.[74-78] Similarly, sulfadiazine appears safe in pregnancy.[79] A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality (specifically kernicterus), compared with infants who received oxytetracycline.[80] Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal use of sulfa (including sulfadiazine) near delivery, although are no studies published to date link late third-trimester maternal sulfa use and neonatal death or kernicterus.

The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AI)**.[36,37] Clindamycin is Food and Drug Administration Pregnancy Category B and considered safe throughout pregnancy. Atovaquone may be used if indicated. While there are limited data on atovaquone safety in humans, preclinical studies have not demonstrated toxicity.[75]

Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented transmission with reactivation of chronic infection in HIV-infected women with severe immunosuppression.[77,81] Pregnant HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis, including TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists **(BIII)**. Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy **(AIII)**.[72] Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in women receiving HAART.[82] Therefore, PCR of amniotic fluid can be considered during gestation in pregnant women on ART with serologic evidence of acquired infection, and also for women with ultrasound findings suggestive of fetal *T. gondii* infection **(BIII)**.[72] Because the risk for transmission with chronic infection appears low, routine fetal evaluation for infection with amniocentesis is not indicated.

Pediatric-care providers should be informed about HIV-infected mothers who have suspected or confirmed *T.*

gondii infection to allow evaluation of their neonates for evidence of congenital infection **(AIII)**.

TMP-SMX can be administered for primary prophylaxis against TE as described for PCP **(AIII)**. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Secondary prophylaxis should be provided, using the same indications as for non-pregnant women. As noted above, pyrimethamine and sulfadiazine are considered safe in pregnancy. Clindamycin may be substituted for sulfadiazine for sulfa-intolerant patients. Dapsone appears to cross the placenta.[83,84] Over the past several decades, dapsone (used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.[84,85] With long-term therapy, there is a risk of mild maternal hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with G6PD deficiency.[86]

Because the odds of perinatal HIV transmission decrease by 6% to 8% per week of ART, clinicians should consider immediate initiation of ART for pregnant women who are diagnosed with TE and not yet on ART **(BIII)**.[87,88] Because in-utero transmission of HIV is associated with HIV viremia at 30 (+/- 4) weeks' gestation, immediate ART is particularly indicated for women who are diagnosed with TE in the third trimester **(AIII)**.[89]

When providing preconception care for HIV-infected women receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued **(BIII)**.

Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 1 of 2)

Preventing First Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm^3 **(AII)**
- *Toxoplasma* seronegative patients receiving a PCP prophylaxis regimen not active against toxoplasmosis should have *toxoplasma* serology retested if CD4 count declines to <100 cells/mm^3 **(CIII)**
- Prophylaxis against toxoplasmosis should be initiated if seroconversion occurred **(AII)**

Note: All the recommended regimens for preventing first episode of toxoplasmosis are also effective in preventing PCP.

Preferred Regimen:

- TMP-SMX 1 DS tablet PO daily **(AII)**

Alternative Regimens:

- TMP-SMX 1 DS tablet PO TIW **(BIII)**, *or*
- TMP-SMX SS tablet PO daily **(BIII)**, *or*
- Dapsone[a] 50 mg PO daily plus (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly **(BI)**, *or*
- (Dapsone[a] 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly **(BI)**, *or*
- Atovaquone[b] 1500 mg PO daily **(CIII)**, *or*
- (Atovaquone[b] 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily **(CIII)**

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >200 cells/mm^3 for >3 months in response to ART **(AI)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <100 to 200 cells/mm^3 **(AIII)**

Treating *Toxoplasma gondii* Encephalitis

Preferred Regimen (AI):

- Pyrimethamine 200 mg PO once, followed by dose based on body weight:

Body Weight ≤60 kg:

- Pyrimethamine 50 mg PO daily plus sulfadiazine 1000 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

Body Weight >60 kg:

- Pyrimethamine 75 mg PO daily plus sulfadiazine 1500 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 2 of 2)

Note: If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine **(BI)**. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies **(BI)**. Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved **(CIII)**.

Alternative Regimens:

- Pyrimethamine (leucovorin)[c] plus clindamycin 600 mg IV or PO q6h **(AI)**; preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine is sulfadiazine; must add additional agent for PCP prophylaxis, *or*
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID **(BI)**, *or*
- Atovaquone[b] 1500 mg PO BID plus pyrimethamine (leucovorin)[c] **(BII)**, *or*
- Atovaquone[b] 1500 mg PO BID plus sulfadiazine[d] **(BII)**, *or*
- Atovaquone[b] 1500 mg PO BID **(BII)**, *or*
- Pyrimethamine (leucovorin)[c] plus azithromycin 900–1200 mg PO daily **(CII)**

Total Duration for Treating Acute Infection:

- At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
- After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below

Chronic Maintenance Therapy for *Toxoplasma gondii* Encephalitis

Preferred Regimen:

- Pyrimethamine 25–50 mg PO daily plus sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) plus leucovorin 10–25 mg PO daily **(AI)**

Alternative Regimens:

- Clindamycin 600 mg PO q8h plus (pyrimethamine 25–50 mg plus leucovorin 10–25 mg) PO daily **(BI)**; must add additional agent to prevent PCP **(AII)**, *or*
- TMP-SMX 1 DS tablet BID **(BII)**, *or*
- TMP-SMX 1 DS tablet daily **(BII)**, *or*
- Atovaquone[b] 750–1500 mg PO BID plus (pyrimethamine 25 mg plus leucovorin 10 mg) PO daily, *or*
- Atovaquone[b] 750–1500 mg PO BID plus sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) **(BII)**, *or*
- Atovaquone[b] 750–1500 mg PO BID **(BII)**

Discontinuing Chronic Maintenance Therapy:

- Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 count >200 cells/mm^3 for >6 months in response to ART **(BI)**

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

- CD4 count <200 cells/mm^3 **(AIII)**

Other Considerations:

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII)**; discontinue as soon as clinically feasible.
- Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continued through at least through the period of acute treatment; anticonvulsants **should not be used** as seizure prophylaxis **(BIII)**.

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

[c] Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for Acute Infection

[d] Sulfadiazine dose: Same as weight-based dose listed in Preferred Regimen for Acute Infection

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; IV = intravenous; PCP = *Pneumocystis* Pneumonia; PO = orally; q(n)h = every "n" hours; SS = single strength; TE = toxoplasmic encephalitis; TIW = three times a week; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. Apr 9 1983;1(8328):781-784. Available at http://www.ncbi.nlm.nih.gov/pubmed/6132129.
2. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med*. Sep 30 1993;329(14):995-1000. Available at http://www.ncbi.nlm.nih.gov/pubmed/8366923.
3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med*. Jan 1984;100(1):36-42. Available at http://www.ncbi.nlm.nih.gov/pubmed/6691657.
4. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of Toxoplasma infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr*. Apr 1993;6(4):414-418. Available at http://www.ncbi.nlm.nih.gov/pubmed/8455146.
5. Mathews WC, Fullerton SC. Use of a clinical laboratory database to estimate Toxoplasma seroprevalence among human immunodeficiency virus-infected patients. Overcoming bias in secondary analysis of clinical records. *Arch Pathol Lab Med*. Aug 1994;118(8):807-810. Available at http://www.ncbi.nlm.nih.gov/pubmed/8060230.
6. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999 2004, decline from the prior decade. *Am J Trop Med Hyg*. Sep 2007;77(3):405-410. Available at http://www.ncbi.nlm.nih.gov/pubmed/17827351.
7. Abgrall S, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. *Clin Infect Dis*. Nov 15 2001;33(10):1747-1755. Available at http://www.ncbi.nlm.nih.gov/pubmed/11595976.
8. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis*. Jan 1996;173(1):91-97. Available at http://www.ncbi.nlm.nih.gov/pubmed/8537688.
9. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. Aug 17 1984;252(7):913-917. Available at http://www.ncbi.nlm.nih.gov/pubmed/6748191.
10. Jones JL, Dargelas V, Roberts J, Press C, Remington JS, Montoya JG. Risk factors for Toxoplasma gondii infection in the United States. *Clin Infect Dis*. Sep 15 2009;49(6):878-884. Available at http://www.ncbi.nlm.nih.gov/pubmed/19663709.
11. Boyer KM, Holfels E, Roizen N, et al. Risk factors for Toxoplasma gondii infection in mothers of infants with congenital toxoplasmosis: Implications for prenatal management and screening. *Am J Obstet Gynecol*. Feb 2005;192(2):564-571. Available at http://www.ncbi.nlm.nih.gov/pubmed/15696004.
12. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magn Reson Imaging*. 1990;8(1):51-57. Available at http://www.ncbi.nlm.nih.gov/pubmed/2325518.
13. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Ann Intern Med*. Oct 15 1995;123(8):594-598. Available at http://www.ncbi.nlm.nih.gov/pubmed/7677300.
14. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. *AJNR Am J Neuroradiol*. Nov 1994;15(10):1885-1894. Available at http://www.ncbi.nlm.nih.gov/pubmed/7863938.
15. Gray F, Gherardi R, Wingate E, et al. Diffuse "encephalitic" cerebral toxoplasmosis in AIDS. Report of four cases. *J Neurol*. Jul 1989;236(5):273-277. Available at http://www.ncbi.nlm.nih.gov/pubmed/2760644.
16. Derouin F, Leport C, Pueyo S, et al. Predictive value of Toxoplasma gondii antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. *AIDS*. Nov 1996;10(13):1521-1527. Available at http://www.ncbi.nlm.nih.gov/pubmed/8931787.
17. Conley FK, Jenkins KA, Remington JS. Toxoplasma gondii infection of the central nervous system. Use of the peroxidase-antiperoxidase method to demonstrate toxoplasma in formalin fixed, paraffin embedded tissue sections. *Hum Pathol*. Aug 1981;12(8):690-698. Available at http://www.ncbi.nlm.nih.gov/pubmed/7026410.
18. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for Toxoplasma gondii DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS*. Dec 1994;8(12):1691-1694. Available at http://www.ncbi.nlm.nih.

gov/pubmed/7888118.

19. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. Jan 1997;11(1):1-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/9110070.
20. Mesquita RT, Ziegler AP, Hiramoto RM, Vidal JE, Pereira-Chioccola VL. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol*. Jun 2010;59(Pt 6):641-647. Available at http://www.ncbi.nlm.nih.gov/pubmed/20150319.
21. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. Mar 1997;48(3):687-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/9065549.
22. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. Feb 1999;17(2):554-560. Available at http://www.ncbi.nlm.nih.gov/pubmed/10080599.
23. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. Jan 15 1999;52(2):253-260. Available at http://www.ncbi.nlm.nih.gov/pubmed/9932940.
24. U.S. Department of Health and Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at http://www.foodsafety.gov. Accessed October 16, 2015.
25. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. Jul 15 1992;117(2):106-111. Available at http://www.ncbi.nlm.nih.gov/pubmed/1351371.
26. Miro JM, Murray HW, Katlama C. Toxoplasmosis. In: Dolin R, ed. AIDS Therapy. 3rd ed. Philadelphia, PA: Churchill Livingstone; 2008:659-681.
27. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. May 15 1995;122(10):755-761. Available at http://www.ncbi.nlm.nih.gov/pubmed/7717598.
28. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. Mar 1995;20(3):531-541. Available at http://www.ncbi.nlm.nih.gov/pubmed/7756472.
29. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. May 27 1993;328(21):1514-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/8479488.
30. Bozzette SA, Finkelstein DM, Spector SA, et al with the NIAID AIDS Clinical Trials Group. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med*. Mar 16 1995;332(11):693-699. Available at http://www.ncbi.nlm.nih.gov/pubmed/7854375.
31. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/10915098.
32. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. Sep 10 1999;13(13):1647-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/10509565.
33. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet*. Jun 24 2000;355(9222):2217-2218. Available at http://www.ncbi.nlm.nih.gov/pubmed/10881897.
34. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. May 2000;181(5):1635-1642. Available at http://www.ncbi.nlm.nih.gov/pubmed/10823763.
35. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary Toxoplasma gondii prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis*. Jul 1 2006;43(1):79-89. Available at http://www.ncbi.nlm.nih.gov/

pubmed/16758422.

36. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. Feb 1996;22(2):268-275. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838183.
37. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. Jan 1 1992;116(1):33-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/1727093.
38. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med*. Jan 1988;84(1):94-100. Available at http://www.ncbi.nlm.nih.gov/pubmed/3337134.
39. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. Sep 1992;6(9):1040-1041. Available at http://www.ncbi.nlm.nih.gov/pubmed/1388895.
40. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for Toxoplasma encephalitis are associated with better outcome. *J Infect Dis*. May 1996;173(5):1294-1295. Available at http://www.ncbi.nlm.nih.gov/pubmed/8627092.
41. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. Jun 1998;42(6):1346-1349. Available at http://www.ncbi.nlm.nih.gov/pubmed/9624473.
42. Beraud G, Pierre-Francois S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994–2006. *Am J Trop Med Hyg*. Apr 2009;80(4):583-587. Available at http://www.ncbi.nlm.nih.gov/pubmed/19346380.
43. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. Aug 2004;24(3):425-443, vi. Available at http://www.ncbi.nlm.nih.gov/pubmed/15242719.
44. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for Pneumocystis carinii pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis*. Apr 1995;20(4):849-853. Available at http://www.ncbi.nlm.nih.gov/pubmed/7795084.
45. Nguyen MT, Weiss PJ, Wallace MR. Two-day oral desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *AIDS*. Jun 1995;9(6):573-575. Available at http://www.ncbi.nlm.nih.gov/pubmed/7662195.
46. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. Oct 15 2001;184(8):992-997. Available at http://www.ncbi.nlm.nih.gov/pubmed/11574913.
47. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol*. Dec 1998;102(6 Pt 1):1033-1036. Available at http://www.ncbi.nlm.nih.gov/pubmed/9847446.
48. Bonfanti P, Pusterla L, Parazzini F, et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study. C.I.S.A.I. Group. *Biomed Pharmacother*. Feb 2000;54(1):45-49. Available at http://www.ncbi.nlm.nih.gov/pubmed/10721462.
49. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. *Clin Infect Dis*. May 1 2002;34(9):1243-1250. Available at http://www.ncbi.nlm.nih.gov/pubmed/11941551.
50. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. Sep 12 1992;340(8820):637-638. Available at http://www.ncbi.nlm.nih.gov/pubmed/1355212.
51. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. Mar 1997;24(3):422-429. Available at http://www.ncbi.nlm.nih.gov/pubmed/9114194.
52. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. *AIDS*. Sep 1996;10(10):1107-1112. Available at http://www.ncbi.nlm.nih.gov/pubmed/8874627.

53. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. Nov 1993;12(11):853-856. Available at http://www.ncbi.nlm.nih.gov/pubmed/8112357.

54. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. Mar 30 2001;15(5):583-589. Available at http://www.ncbi.nlm.nih.gov/pubmed/11316995.

55. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. Oct 1991;35(10):2049-2052. Available at http://www.ncbi.nlm.nih.gov/pubmed/1836943.

56. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. Jan 1993;7(1):143-144. Available at http://www.ncbi.nlm.nih.gov/pubmed/8442914.

57. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-Toxoplasma effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother*. Feb 1991;35(2):252-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/2024957.

58. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother*. Jan 1995;39(1):276-277. Available at http://www.ncbi.nlm.nih.gov/pubmed/7695324.

59. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis*. 1993;25(1):157-160. Available at http://www.ncbi.nlm.nih.gov/pubmed/8460343.

60. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/pubmed/19440326.

61. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. Jul 28 2009;73(4):321-322. Available at http://www.ncbi.nlm.nih.gov/pubmed/19636053.

62. Tremont-Lukats IW, Garciarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. May 5 2009;150(9):656-657. Available at http://www.ncbi.nlm.nih.gov/pubmed/19414855.

63. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. Jun 2011;82(6):691-693. Available at http://www.ncbi.nlm.nih.gov/pubmed/20660912.

64. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. Feb 2004;48(2):635-637. Available at http://www.ncbi.nlm.nih.gov/pubmed/14742225.

65. Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. *Eur J Clin Microbiol Infect Dis*. Feb 2000;19(2):89-95. Available at http://www.ncbi.nlm.nih.gov/pubmed/10746493.

66. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. Dec 24 1998;339(26):1889-1895. Available at http://www.ncbi.nlm.nih.gov/pubmed/9862944.

67. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. Jun 18 2004;18(9):1342-1344. Available at http://www.ncbi.nlm.nih.gov/pubmed/15362670.

68. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. 2004; 18:1342-4.

69. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Mar 10 2000;14(4):383-386. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770540.

70. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. Jul 2006;12(7):666-671. Available at http://www.ncbi.nlm.nih.gov/pubmed/16774564.

71. Montoya JG. Laboratory diagnosis of Toxoplasma gondii infection and toxoplasmosis. *J Infect Dis*. Feb 15 2002;185 Suppl 1:S73-82. Available at http://www.ncbi.nlm.nih.gov/pubmed/11865443.

72. Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. *Clin Infect Dis*. Aug 15 2008;47(4):554-566. Available at http://www.ncbi.nlm.nih.gov/pubmed/18624630.

73. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. *Pediatr Infect Dis J*. Jul 1990;9(7):512-518. Available at http://www.ncbi.nlm.nih.gov/pubmed/2371084.

74. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at http://www.ncbi.nlm.nih.gov/pubmed/17536875.

75. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. Jan 2006;1(1):1-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/18690910.

76. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. Jun 1994;18(6):853-861; quiz 862. Available at http://www.ncbi.nlm.nih.gov/pubmed/8086543.

77. Dunn CS, Beyer C, Kieny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. *Virology*. Sep 15 1996;223(2):351-361. Available at http://www.ncbi.nlm.nih.gov/pubmed/8806570.

78. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. Jul-Aug 2001;95(4):424-428. Available at http://www.ncbi.nlm.nih.gov/pubmed/11579889.

79. Baskin CG, Law S, Wenger NK. Sulfadiazine rheumatic fever prophylaxis during pregnancy: does it increase the risk of kernicterus in the newborn? *Cardiology*. 1980;65(4):222-225. Available at http://www.ncbi.nlm.nih.gov/pubmed/7388849.

80. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. Oct 1956;18(4):614-625. Available at http://www.ncbi.nlm.nih.gov/pubmed/13370229.

81. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. *Eur J Obstet Gynecol Reprod Biol*. Sep 1996;68(1-2):93-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/8886688.

82. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*. Feb 2009;200(2):160 e161-169. Available at http://www.ncbi.nlm.nih.gov/pubmed/18986640.

83. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. Jul-Aug 1986;11(4):299-315. Available at http://www.ncbi.nlm.nih.gov/pubmed/3530584.

84. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at http://www.ncbi.nlm.nih.gov/pubmed/15230645.

85. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Trop Med Int Health*. Jun 2003;8(6):488-506. Available at http://www.ncbi.nlm.nih.gov/pubmed/12791054.

86. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. May 1989;82(5):668. Available at http://www.ncbi.nlm.nih.gov/pubmed/2717998.

87. Hoffman RM, Black V, Technau K, et al. Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. *J Acquir Immune Defic Syndr*. May 1 2010;54(1):35-41. Available at http://www.ncbi.nlm.nih.gov/pubmed/20216425.

88. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. Jan 11 2008;22(2):289-299. Available at http://www.ncbi.nlm.nih.gov/pubmed/18097232.

89. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. Feb 15 2010;50(4):585-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/20070234.

Cryptosporidiosis (Last updated June 17, 2013; last reviewed June 14, 2017)

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa and, if symptomatic, typically cause diarrhea. *Cryptosporidium* can also infect other gastrointestinal and extraintestinal sites, especially in individuals whose immune systems are suppressed. Advanced immunosuppression—typically CD4 T lymphocyte cell (CD4) counts of <100 cells/μL[1]—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis. The three species that most commonly infect humans are *Cryptosporidium hominis*, *Cryptosporidium parvum*, and *Cryptosporidium meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.[2]

Cryptosporidiosis remains a common cause of chronic diarrhea in AIDS patients in developing countries, with up to 74% of diarrheal stools demonstrating the organism.[3] In developed countries with low rates of environmental contamination and where potent antiretroviral therapy (ART) is widely available, cryptosporidiosis has decreased and occurs at an incidence of <1 case per 1000 person-years in patients with AIDS.[4] Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with infected humans or animals, particularly those with diarrhea. Oocysts can contaminate recreational water sources such as swimming pools and lakes, and public water supplies and may persist despite standard chlorination (see Appendix: Food and Water-Related Exposures). Person-to-person transmission is common, especially among sexually active men who have sex with men.

Clinical Manifestations

Patients with cryptosporidiosis most commonly have acute or subacute onset of watery diarrhea, which may be accompanied by nausea, vomiting, and lower abdominal cramping. Severity can range from asymptomatic to profuse, cholera-like diarrhea. More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhea alone is typical in hosts with competent immune systems. Fever is present in approximately one-third of patients and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium*, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4 cell counts.[5-8] Pulmonary infections also have been reported,[9,10] and may be under-recognized.[11]

Diagnosis

Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue with acid-fast staining or direct immunofluorescence, which offers better sensitivity.[12] Immunofluorescence is estimated to be 10 times more sensitive than acid-fast staining and is now the gold standard for stool examination. Concentration methods (i.e., formalin ether or formalin-ethyl acetate) and flotation methods (i.e., Sheather's sucrose or sodium chloride) may facilitate diagnosis, but they are very labor intensive and not routinely used in clinical laboratories. Antigen-detection by enzyme-linked immunosorbent assay or immunochromatographic tests also are useful, with sensitivities reportedly ranging from 66% to 100%, depending on the specific test. Molecular methods such as polymerase chain reaction (PCR) are even more sensitive,[13] detecting as few as five oocysts in spiked stool samples and nearly double the number of cases identified by microscopic methods. Cryptosporidial enteritis also can be diagnosed from small sections from intestinal biopsy.

A single stool specimen is usually adequate for diagnosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

Preventing Exposure

HIV-infected individuals should be educated and counseled about the different ways that *Cryptosporidium* can be transmitted **(BIII)**. Modes of transmission include having direct contact with infected adults, diaper-aged children, and infected animals; coming into contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Detailed prevention recommendations related to food and water exposures (including methods for removing *Cryptosporidium* from drinking water), pet exposures, and travel-related exposures can be found in Appendix A: Recommendations to Help HIV-infected Patients Avoid Exposure to, or Infection from, Opportunistic Pathogens.

Scrupulous handwashing can reduce the risk of diarrhea in HIV-infected individuals, including diarrhea caused by *Cryptosporidium*.[14] HIV-infected patients should be advised to wash their hands after potential contact with human feces (including after diapering small children). Hand-washing also should be recommended in association with the following activities: after handling pets or other animals, gardening or having other contact with soil; before preparing food or eating; and before and after sex **(BIII)**. HIV-infected patients should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces. They should be advised to use barriers such as condoms and dental dams during sex to reduce such exposures **(BIII)**.

HIV-infected individuals—particularly those with CD4 counts <200 cells/μL—should avoid direct contact with diarrhea or stool from pets **(BIII)**. Gloves should be worn when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. They should also limit or avoid direct exposure to calves and lambs **(BII)**. Paying attention to hygiene and avoiding direct contact with stool are important when visiting premises such as farms or petting zoos where these animals are housed or exhibited.

HIV-infected individuals should not drink water directly from lakes or rivers **(AIII)**. Waterborne infection also can result from swallowing water during recreational activities. HIV-infected individuals should be made aware that lakes, rivers, and salt water beaches and some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water **(BIII)**.

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations that impose a community advisory to boil water, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis **(AIII)**. Using submicron personal-use water filters (home/office types) or bottled water also may reduce the risk of infection from municipal and well water **(BII)**.

For persons with low CD4 cell counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain, and available data are inadequate to recommend that all HIV-infected persons boil water or avoid drinking tap water in non-outbreak settings. However, HIV-infected individuals should consider drinking only filtered water **(CIII)**, despite the complexities involved in selecting appropriate products, the lack of enforceable standards for removal of oocysts, the costs of the products, and the logistic difficulty of using these products consistently. Note that ice made from contaminated tap water also can be a source of infection.

HIV-infected patients with low CD4 cell counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for longer than 2 months and have been found in oysters taken from certain commercial oyster beds **(CIII)**. In the hospital setting, standard precautions for use of gloves and for hand-washing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected individual **(BIII)**. Because of the potential for fomite transmission, some specialists recommend that HIV-infected patients, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII)**.

HIV-infected individuals who travel to developing countries should be warned to avoid drinking tap water or

using tap water to brush their teeth **(BIII)**. Ice that is not made from bottled water and consumption of raw fruits or vegetables that could have been washed in tap water should also be avoided **(BIII)**. HIV-infected individuals also should avoid other sources of *Cryptosporidium* oocysts as much as possible **(BIII)**. These include working directly with people with diarrhea; with farm animals such as cattle and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, gloves should be used and practices for good hand hygiene observed.

Preventing Disease

Because chronic cryptosporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination ART before the patient becomes severely immunosuppressed should prevent this disease **(AII)**. Rifabutin and possibly clarithromycin, when taken for *Mycobacterium avium complex* prophylaxis, have been found to protect against cryptosporidiosis.[15,16] Data are insufficient, however, to warrant a recommendation for using rifabutin or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treating Disease

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/μL usually leads to resolution of clinical cryptosporidiosis[17-21] and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be started on ART as part of the initial management of their infection **(AII)**. HIV protease inhibitors (PIs) can inhibit *Cryptosporidium in vitro* and in animal models, and some experts believe that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23] Management should also include symptomatic treatment of diarrhea with anti-motility agents **(AIII)**. Tincture of opium may be more effective than loperamide **(CIII)**. Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved to treat secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents and is usually **not** recommended **(CII)**.[24] Because diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions **(AIII)**.

Patients with biliary tract involvement may require endoscopic retrograde choledocoduodenoscopy for diagnosis. They may also benefit from sphincterotomy and/or stenting.[25]

Several agents have been investigated in small, randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[19]

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa.[26,27] It is approved by the U.S. Food and Drug Administration for treatment of cryptosporidiosis in children and adults. When administered for 3 days at 500 mg twice daily to HIV-uninfected adults with cryptosporidiosis, nitazoxanide resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[26] In one study, HIV-infected adults with cryptosporidiosis with CD4 counts >50 cells/μL were treated with nitazoxanide 500 to 1000 mg twice daily for 14 days; they experienced substantially higher rates of parasitological cure and resolution of diarrhea than those in the placebo group.[27] This finding was not confirmed, however, in two randomized trials in children.[28,29] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts less than 50 cells/μL, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.[30] Adverse events associated with nitazoxanide are limited and typically mild, and no important drug-drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, a trial

of nitazoxanide or other anti-parasitic drugs in conjunction with ART, but never instead of ART, can be considered **(CIII)**.

Paromomycin is a non-absorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. It is effective in high doses for the treatment of cryptosporidiosis in animal models.[31] A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, relapses were common, with long-term success rates of only 33%.[25] Two randomized trials comparing paromomycin with placebo among patients with AIDS and cryptosporidiosis showed that the drug had limited effectiveness in patients with AIDS,[32,33] and a meta-analysis of the two trials found the drug was not significantly more effective than placebo at reducing diarrheal frequency or parasite burden, but that analysis was limited by the small sample size and methodologic problems.[19] One case series suggested a better response rate in patients receiving paromomycin along with ART.[34] Paromomycin may be used instead of nitazoxanide along with, but never instead of ART **(CIII)**.

Special considerations with regard to starting ART

As noted above, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection **(AII)**. PIs can inhibit *Cryptosporidium in vitro* and in animal models, thus some authorities feel that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23]

Monitoring of response to therapy and adverse events (including IRIS)

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte imbalance, weight loss, and malnutrition. Total parenteral nutrition may be indicated in certain patients **(CIII)**. Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with treatment of cryptosporidiosis.

Managing treatment failure

Supportive treatment and optimization of ART to achieve full virologic suppression are the only feasible approaches to managing treatment failure **(AIII)**.

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in non-pregnant women **(AII)**. Pregnancy should not preclude the use of ART and in fact is always an indication for ART.[35] Nitazoxanide is not teratogenic in animals but no human data on use in pregnancy are available. Nitazoxanide can be used in pregnancy after the first trimester in women with severe symptoms **(CIII)**. Limited information is available about the teratogenic potential of paromomycin, but oral administration is associated with minimal systemic absorption, which may minimize potential risk. Paromomycin can be used in pregnancy after the first trimester in women with severe symptoms **(CIII)**. Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, a recent study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[36] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII)**. Loperamide is the preferred anti-motility agent in late pregnancy **(CIII)**. Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal, therefore tincture of opium is **not** recommended in late pregnancy **(AIII)**.

Recommendations for Preventing and Managing Cryptosporidiosis

Preventing Chronic Cryptosporidiosis

- Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

Managing Cryptosporidiosis

Preferred Management Strategies:

- Initiate or optimize ART for immune restoration to CD4 count >100 cells/mm^3 **(AII)**.
- Aggressive oral and/or IV rehydration and replacement of electrolyte loss **(AIII)**, and symptomatic treatment of diarrhea with anti-motility agent **(AIII)**.
- Tincture of opium may be more effective than loperamide as an anti-diarrheal agent **(CIII)**.

Alternative Management Strategies:

No therapy has been shown to be effective without ART. Trial of these agents may be used in conjunction with, but not instead of, ART:

- Nitazoxanide 500–1000 mg PO BID with food for 14 days **(CIII)** + optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or alternatively*
- Paromomycin 500 mg PO QID for 14 to 21 days (**CIII)** + optimized ART, symptomatic treatment and rehydration and electrolyte replacement

Other Considerations:

- Since diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

Key to Acronyms: ART = antiretroviral therapy; IV = intraveneously; PO = orally; BID = twice a day; QID = four times a day

References

1. Flanigan T, Whalen C, Turner J, et al. *Cryptosporidium* infection and CD4 counts. *Ann Intern Med*. May 15 1992;116(10):840-842. Available at http://www.ncbi.nlm.nih.gov/pubmed/1348918.
2. Cama V, Gilman RH, Vivar A, et al. Mixed *Cryptosporidium* infections and HIV. *Emerg Infect Dis*. Jun 2006;12(6):1025-1028. Available at http://www.ncbi.nlm.nih.gov/pubmed/16707069.
3. Tumwine JK, Kekitiinwa A, Bakeera-Kitaka S, et al. Cryptosporidiosis and microsporidiosis in Ugandan children with persistent diarrhea with and without concurrent infection with the human immunodeficiency virus. *Am J Trop Med Hyg*. Nov 2005;73(5):921-925. Available at http://www.ncbi.nlm.nih.gov/pubmed/16282304.
4. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. Jun 19 2010;24(10):1549-1559. Available at http://www.ncbi.nlm.nih.gov/pubmed/20502317.
5. Ducreux M, Buffet C, Lamy P, et al. Diagnosis and prognosis of AIDS-related cholangitis. *AIDS*. Aug 1995;9(8):875-880. Available at http://www.ncbi.nlm.nih.gov/pubmed/7576321.
6. Chen XM, LaRusso NF. Cryptosporidiosis and the pathogenesis of AIDS-cholangiopathy. *Semin Liver Dis*. Aug 2002;22(3):277-289. Available at http://www.ncbi.nlm.nih.gov/pubmed/12360421.
7. Chen C, Gulati P, French SW. Pathologic quiz case: a patient with acquired immunodeficiency syndrome and an unusual biliary infection. *Arch Pathol Lab Med.* Feb 2003;127(2):243-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/12562247.
8. de Souza Ldo R, Rodrigues MA, Morceli J, Kemp R, Mendes RP. Cryptosporidiosis of the biliary tract mimicking pancreatic cancer in an AIDS patient. *Rev Soc Bras Med Trop*. Mar-Apr 2004;37(2):182-185. Available at http://www.ncbi.nlm.nih.gov/pubmed/15094908.
9. Moore JA, Frenkel JK. Respiratory and enteric cryptosporidiosis in humans. *Arch Pathol Lab Med*. Nov 1991;115(11):1160-1162. Available at http://www.ncbi.nlm.nih.gov/pubmed/1747035.
10. Mercado R, Buck GA, Manque PA, Ozaki LS. *Cryptosporidium hominis* infection of the human respiratory tract. *Emerg Infect Dis*. Mar 2007;13(3):462-464. Available at http://www.ncbi.nlm.nih.gov/pubmed/17552101.
11. Mor SM, Tumwine JK, Ndeezi G, et al. Respiratory cryptosporidiosis in HIV-seronegative children in Uganda: potential

for respiratory transmission. *Clin Infect Dis*. May 15 2010;50(10):1366-1372. Available at http://www.ncbi.nlm.nih.gov/pubmed/20377408.

12. Weber R, Bryan RT, Bishop HS, Wahlquist SP, Sullivan JJ, Juranek DD. Threshold of detection of Cryptosporidium oocysts in human stool specimens: evidence for low sensitivity of current diagnostic methods. *J Clin Microbiol*. Jul 1991;29(7):1323-1327. Available at http://www.ncbi.nlm.nih.gov/pubmed/1715881.
13. Nair P, Mohamed JA, DuPont HL, et al. Epidemiology of cryptosporidiosis in North American travelers to Mexico. *Am J Trop Med Hyg*. Aug 2008;79(2):210-214. Available at http://www.ncbi.nlm.nih.gov/pubmed/18689626.
14. Huang DB, Zhou J. Effect of intensive handwashing in the prevention of diarrhoeal illness among patients with AIDS: a randomized controlled study. *J Med Microbiol*. May 2007;56(Pt 5):659-663. Available at http://www.ncbi.nlm.nih.gov/pubmed/17446290.
15. Holmberg SD, Moorman AC, Von Bargen JC, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. HIV Outpatient Study (HOPS) Investigators. *JAMA*. Feb 4 1998;279(5):384-386. Available at http://www.ncbi.nlm.nih.gov/pubmed/9459473.
16. Fichtenbaum CJ, Zackin R, Feinberg J, Benson C, Griffiths JK, Team ACTGNWCS. Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. *AIDS*. Dec 22 2000;14(18):2889-2893. Available at http://www.ncbi.nlm.nih.gov/pubmed/11153670.
17. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet*. Jan 24 1998;351(9098):256-261. Available at http://www.ncbi.nlm.nih.gov/pubmed/9457096.
18. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. Oct 1 2000;25(2):124-129. Available at http://www.ncbi.nlm.nih.gov/pubmed/11103042.
19. Cabada MM, White AC, Jr. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis*. Oct 2010;23(5):494-499. Available at http://www.ncbi.nlm.nih.gov/pubmed/20689422.
20. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. Jun 2009;80(6):1060-1064. Available at http://www.ncbi.nlm.nih.gov/pubmed/19478276.
21. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. Mar 2000;19(3):213-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/10795595.
22. Mele R, Gomez Morales MA, Tosini F, Pozio E. Indinavir reduces *Cryptosporidium parvum* infection in both in vitro and in vivo models. *Int J Parasitol.* Jul 2003;33(7):757-764. Available at http://www.ncbi.nlm.nih.gov/pubmed/12814654.
23. Hommer V, Eichholz J, Petry F. Effect of antiretroviral protease inhibitors alone, and in combination with paromomycin, on the excystation, invasion and in vitro development of *Cryptosporidium parvum*. *J Antimicrob Chemother.* Sep 2003;52(3):359-364. Available at http://www.ncbi.nlm.nih.gov/pubmed/12888587.
24. Simon DM, Cello JP, Valenzuela J, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. *Gastroenterology*. Jun 1995;108(6):1753-1760. Available at http://www.ncbi.nlm.nih.gov/pubmed/7768380.
25. Hashmey R, Smith NH, Cron S, Graviss EA, Chappell CL, White AC, Jr. Cryptosporidiosis in Houston, Texas. A report of 95 cases. *Medicine (Baltimore)*. Mar 1997;76(2):118-139. Available at http://www.ncbi.nlm.nih.gov/pubmed/9100739.
26. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. Jul 1 2001;184(1):103-106. Available at http://www.ncbi.nlm.nih.gov/pubmed/11398117.
27. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. *Trans R Soc Trop Med Hyg*. Nov-Dec 1998;92(6):663-666. Available at http://www.ncbi.nlm.nih.gov/pubmed/10326116.
28. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*. Nov 2 2002;360(9343):1375-1380. Available at http://www.ncbi.nlm.nih.gov/pubmed/12423984.

29. Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis*. 2009;9:195. Available at http://www.ncbi.nlm.nih.gov/pubmed/19954529.

30. Rossignol JF. Nitazoxanide in the treatment of acquired immune deficiency syndrome-related cryptosporidiosis: results of the United States compassionate use program in 365 patients. *Aliment Pharmacol Ther*. Sep 1 2006;24(5):887-894. Available at http://www.ncbi.nlm.nih.gov/pubmed/16918894.

31. Tzipori S, Rand W, Griffiths J, Widmer G, Crabb J. Evaluation of an animal model system for cryptosporidiosis: therapeutic efficacy of paromomycin and hyperimmune bovine colostrum-immunoglobulin. *Clin Diagn Lab Immunol*. Jul 1994;1(4):450-463. Available at http://www.ncbi.nlm.nih.gov/pubmed/8556484.

32. White AC, Jr., Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. *J Infect Dis*. Aug 1994;170(2):419-424. Available at http://www.ncbi.nlm.nih.gov/pubmed/8035029.

33. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trial Group. *Clin Infect Dis*. Oct 2000;31(4):1084-1092. Available at http://www.ncbi.nlm.nih.gov/pubmed/11049793.

34. Maggi P, Larocca AM, Ladisa N, et al. Opportunistic parasitic infections of the intestinal tract in the era of highly active antiretroviral therapy: is the CD4(+) count so important? *Clin Infect Dis*. Nov 1 2001;33(9):1609-1611. Available at http://www.ncbi.nlm.nih.gov/pubmed/11588705.

35. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on March 4, 2013.

36. Kallen B, Nilsson E, Otterblad Olausson P. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr*. May 2008;97(5):541-545. Available at http://www.ncbi.nlm.nih.gov/pubmed/18394096.

Microsporidiosis (Last updated May 7, 2013; last reviewed June 14, 2017)

Epidemiology

Microsporidia are protists related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore. They are ubiquitous organisms and are likely zoonotic and/or waterborne in origin. The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon* (*syn Septata*) *intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *P. ronneafiei*, *Vittaforma* (syn *Nosema*) *corneae*, *Microsporidium* sp, *Nosema ocularum*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, and *Anncaliia* (syns *Brachiola/Nosema*) *algerae*.[1-7] In the pre-antiretroviral (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among HIV-infected patients with diarrhea, depending on the diagnostic techniques employed and the patient population described.[2-4,7] The incidence of microsporidiosis has declined with the widespread use of effective ART, but continues to occur among HIV-infected patients who are unable to obtain ART or to remain on it.[8] Microsporidiosis is increasingly recognized among HIV-uninfected persons, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In patients with immune suppression, clinical signs related to microsporidiosis are most commonly observed when CD4 T lymphocyte cell (CD4) counts are <100 cells/μL.[2-4,7]

Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection have also been described.[2-4,7]

Clinical syndromes can vary by infecting species. *E. bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Anncaliia* and *Trachipleistophora* are associated with keratoconjunctivitis. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Effective morphologic demonstration of microsporidia by light microscopy can be accomplished with staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples such as stool. In addition, because of the small size of the spores (1–5 mm), magnification up to 1,000 times is required for visualization. Chromotrope 2R and the fluorescent brighteners calcofluor white and Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.[6]

In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown-Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin-Starry silver staining, or Chromotrope 2A.[6] In gastrointestinal disease, examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy may be useful. If the etiologic agent is *Encephalitozoon* or *Trachipleistophora* sp., examination of urine often also reveals the organism. Determination of the species of microsporidia causing disease can be made by the morphology of the organism demonstrated by transmission electron microscopy, by staining with species-specific antibodies, or by polymerase chain

reaction using species- or genus-specific primers.[6,9] Assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

Patients with AIDS who have CD4 counts <200 cells/µL should avoid untreated water sources **(AIII)**. Additional recommendations include general attention to hand washing and personal hygiene, avoiding eating undercooked meat or seafood, and limiting exposure to animals known to be infected with microsporidia **(BIII)**.[10] The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis (see also Appendix: Food and Water-Related Exposures).

Preventing Disease

Because chronic microsporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination ART before the patient becomes severely immunosuppressed should prevent this disease **(AII)**. No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Data suggest that treatment with ART enables a patient's own defenses to eradicate microsporidia,[11,12] and administration of ART with immune restoration (an increase in CD4 count to >100 cells/µL) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *E. bieneusi*.[11-14] All patients therefore should be offered ART as part of the initial management of microsporidial infection **(AII)**. They should be given fluid support if they have signs of diarrhea and dehydration **(AII)**. Patients with malnutrition and wasting should be treated with nutritional supplementation **(AIII)**. Antimotility agents can be used if required for diarrhea control **(BIII)**.

No specific therapeutic agent is available for *E. bieneusi* infection. A controlled clinical trial suggested that *E. bieneusi* infection may respond to oral fumagillin (60 mg/day), a water-insoluble antibiotic made by *Aspergillus fumigatus* **(BII)**,[15,16] or to its synthetic analog, TNP-470 **(BIII)**.[17] However, fumagillin and TNP-470 are not available for systemic use in the United States. One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;[18] however, the effect appeared to be minimal among patients with low CD4 cell counts. Therefore, this drug **cannot be recommended** with confidence **(CIII)**.

Albendazole, a benzimidazole that binds to β-tubulin, has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *V. corneae*. The tubulin genes of both *E. bieneusi*[19] and *V corneae*[20] have amino acid residues associated with albendazole resistance. Albendazole is only recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII)**.[21-23]

Itraconazole may be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* **(CIII)**. Treatment with furazolidone (an agent that is not currently available in the United States) combined with albendazole was reported to improve clinical signs in four HIV-infected patients with persistent diarrhea and *E. bieneusi* infection **(CIII)**;[24] however, furazolidone has not been demonstrated to be active in other case reports. Metronidazole and atovaquone are not active *in vitro* or in animal models and **should not be used** to treat microsporidiosis **(AII)**.

Ocular infections caused by microsporidia should be treated with topical Fumidil B (fumagillin bicylohexylammonium) in saline (to achieve a concentration of 70 µg/mL of fumagillin) **(BII)**.[21] Topical fumagillin is the only formulation available for treatment in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in urine or in nasal smears. Therefore, the use of albendazole as a

companion systemic agent to fumagillin is recommended in ocular infections **(BIII)**.

Special Considerations with Regard to Starting ART

As noted above, all patients should be offered ART as part of the initial management of microsporidial infection and also fluid support if they have signs of diarrhea and dehydration **(AII)**. Data suggest that treatment with ART, which results in immune reconstitution, enables a patient's own defenses to eradicate microsporidia.[11,12]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Although side effects with albendazole are rare, hepatic enzymes should be monitored because elevations have been reported. Albendazole is not known to be carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible on stopping the drug.

One report of immune reconstitution inflammatory syndrome (IRIS) has been described in an HIV-infected patient treated with ART in the setting of *E. bieneusi* infection;[25] however, no IRIS reactions have been reported with other species of microsporidia or with other cases of *E. bieneusi*. Concerns about IRIS should not alter therapy or the institution of ART **(AIII)**.

Managing Treatment Failure

Supportive treatment and optimization of ART to attempt to achieve full virologic suppression are the only currently feasible approaches to managing treatment failure **(AIII)**.

Preventing Recurrence

In individuals with relatively competent immune systems (>200 CD4 cells/μL blood), treatment can probably be discontinued after ocular infection resolves **(CIII)**, but it should be continued indefinitely if CD4 counts fall below 200 cells/μL blood because recurrence or relapse may occur after treatment discontinuation **(BIII)**. Whether it is safe to discontinue treatment for other manifestations after immune restoration with ART is unknown. Based on experience with discontinuation of secondary prophylaxis for other opportunistic infections, it is reasonable to discontinue chronic maintenance therapy in patients who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to levels >200 cells/μL for 6 months after ART **(BIII)**.[12]

Special Considerations During Pregnancy

Rehydration and initiation of ART should be the mainstays of initial treatment of cryptosporidiosis during pregnancy, as in nonpregnant women **(AII)**. In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than that estimated with therapeutic human dosing. There are no adequate and well-controlled studies of albendazole exposure in early human pregnancy. A recent randomized trial in which albendazole was used for second-trimester treatment of soil-transmitted helminth infections found no evidence of teratogenicity or other adverse pregnancy effects.[26]

Based on these data, albendazole **is not recommended** for use during the first trimester **(BIII)**; use in later pregnancy should be considered only if benefits are felt to outweigh potential risk **(CIII)**. Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the antiangiogenic effect of fumagillin, this drug **should not be used** systemically in pregnant women **(AIII)**. Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate **(CIII)**. Furazolidone is not teratogenic in animal studies, but human data are limited to a case series that found no association between first-trimester use of furazolidone and birth defects in 132 exposed pregnancies.[27] Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of

more than 300 women with first-trimester exposure did not show an increased risk of malformation.[28,29] In general, however, azole antifungals should be avoided during the first trimester **(BIII)**. Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, a recent study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[30] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII)**. Loperamide is the preferred antimotility agent in late pregnancy **(CIII)**. Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal, therefore tincture of opium **is not recommended** in late pregnancy **(AIII)**.

Recommendations for Managing Microsporidiosis

Preventing Chronic Microsporidiosis

- Because chronic microsporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

Managing Microsporidiosis

- Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 **(AII)**.
- Severe dehydration, malnutrition, and wasting should be managed by fluid support **(AII)** and nutritional supplements **(AIII)**.
- Anti-motility agents can be used for diarrhea control, if required **(BIII)**.

For Gastrointestinal Infections Caused by Enterocytozoon bieneusi

- The best treatment option is ART and fluid support **(AII)**.
- No specific therapeutic agent is available for this infection.
- Fumagillin 60 mg PO daily **(BII)** and TNP-470 **(BIII)** are two agents that have some effectiveness, but neither agent is available in the United States.
- Nitazoxanide may have some effect, but the efficacy is minimal in patients with low CD4 cell count, and cannot be recommended **(CIII)**.

For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than E. bieneusi *and* Vittaforma corneae:

- Albendazole 400 mg PO BID **(AII)**, continue until CD4 count >200 cells/mm^3 for >6 months after initiation of ART **(BIII)**

For Disseminated Disease Caused by Trachipleistophora *or* Anncaliia

- Itraconazole 400 mg PO daily + albendazole 400 mg PO BID **(CIII)**

For Ocular Infection:

- Topical fumagillin bicylohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops—2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **(BII)**, plus albendazole 400 mg PO BID for management of systemic infection **(BIII)**
- For patients with CD4 count >200 cells/mm^3, therapy can probably be discontinued after ocular infection resolves **(CIII)**.
- For patients with CD4 count ≤200 cells/mm^3, therapy should be continued until resolution of ocular symptoms and CD4 count increases to >200 cells/uL for at least 6 months in response to ART **(BIII)**

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; PO = orally, QID = four times daily

References

1. Beauvais B, Sarfati C, Molina JM, Lesourd A, Lariviere M, Derouin F. Comparative evaluation of five diagnostic methods for demonstrating microsporidia in stool and intestinal biopsy specimens. *Ann Trop Med Parasitol*. Feb 1993;87(1):99-102. Available at http://www.ncbi.nlm.nih.gov/pubmed/8346996.
2. Deplazes P, Mathis A, Weber R. Epidemiology and zoonotic aspects of microsporidia of mammals and birds. *Contributions to Microbiology*. 2000;6:236-260. Available at http://www.ncbi.nlm.nih.gov/pubmed/10943515.
3. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Advances in Parasitology*. 1998;40:321-349. Available at http://www.ncbi.nlm.nih.gov/pubmed/9554078.
4. Mathis A. Microsporidia: emerging advances in understanding the basic biology of these unique organisms.

International Journal for Parasitology. Jun 2000;30(7):795-804. Available at http://www.ncbi.nlm.nih.gov/pubmed/10899524.

5. Weber R, Bryan RT, Owen RL, Wilcox CM, Gorelkin L, Visvesvara GS. Improved light-microscopical detection of microsporidia spores in stool and duodenal aspirates. The Enteric Opportunistic Infections Working Group. *N Engl J Med*. Jan 16 1992;326(3):161-166. Available at http://www.ncbi.nlm.nih.gov/pubmed/1370122.
6. Weiss LM, Vossbrinck CR. Microsporidiosis: molecular and diagnostic aspects. *Advances in Parasitology*. 1998;40:351-395. Available at http://www.ncbi.nlm.nih.gov/pubmed/9554079.
7. Wittner M, Weiss L. *The Microsporidia and Microsporidiosis*. Washington DC: ASM Press; 1999.
8. Stark D, Barratt JL, van Hal S, Marriott D, Harkness J, Ellis JT. Clinical significance of enteric protozoa in the immunosuppressed human population. *Clin Microbiol Rev*. Oct 2009;22(4):634-650. Available at http://www.ncbi.nlm.nih.gov/pubmed/19822892.
9. Sheoran AS, Feng X, Singh I, et al. Monoclonal antibodies against Enterocytozoon bieneusi of human origin. *Clin Diagn Lab Immunol*. Sep 2005;12(9):1109-1113. Available at http://www.ncbi.nlm.nih.gov/pubmed/16148179.
10. Didier ES, Weiss LM. Microsporidiosis: current status. *Curr Opin Infect Dis*. Oct 2006;19(5):485-492. Available at http://www.ncbi.nlm.nih.gov/pubmed/16940873.
11. Goguel J, Katlama C, Sarfati C, Maslo C, Leport C, Molina JM. Remission of AIDS-associated intestinal microsporidiosis with highly active antiretroviral therapy. *AIDS*. Nov 1997;11(13):1658-1659. Available at http://www.ncbi.nlm.nih.gov/pubmed/9365777.
12. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. Oct 1 2000;25(2):124-129. Available at http://www.ncbi.nlm.nih.gov/pubmed/11103042.
13. Conteas CN, Berlin OG, Speck CE, Pandhumas SS, Lariviere MJ, Fu C. Modification of the clinical course of intestinal microsporidiosis in acquired immunodeficiency syndrome patients by immune status and anti-human immunodeficiency virus therapy. *Am J Trop Med Hyg*. May 1998;58(5):555-558. Available at http://www.ncbi.nlm.nih.gov/pubmed/9598440.
14. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. Mar 2000;19(3):213-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/10795595.
15. Molina J, J G, Sarfati C. Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection (Letter). *AIDS*. 2000;14:1341-1348.
16. Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med*. Jun 20 2002;346(25):1963-1969. Available at http://www.ncbi.nlm.nih.gov/pubmed/12075057.
17. Didier PJ, Phillips JN, Kuebler DJ, et al. Antimicrosporidial activities of fumagillin, TNP-470, ovalicin, and ovalicin derivatives *in vitro* and *in vivo*. *Antimicrob Agents Chemother*. Jun 2006;50(6):2146-2155. Available at http://www.ncbi.nlm.nih.gov/pubmed/16723577.
18. Bicart-See A, Massip P, Linas MD, Datry A. Successful treatment with nitazoxanide of Enterocytozoon bieneusi microsporidiosis in a patient with AIDS. *Antimicrob Agents Chemother*. Jan 2000;44(1):167-168. Available at http://www.ncbi.nlm.nih.gov/pubmed/10602740.
19. Akiyoshi DE, Weiss LM, Feng X, et al. Analysis of the beta-tubulin genes from Enterocytozoon bieneusi isolates from a human and rhesus macaque. *The Journal of Eukaryotic Microbiology*. Jan-Feb 2007;54(1):38-41. Available at http://www.ncbi.nlm.nih.gov/pubmed/17300517.
20. Franzen C, Salzberger B. Analysis of the beta-tubulin gene from *Vittaforma corneae* suggests benzimidazole resistance. *Antimicrob Agents Chemother*. Feb 2008;52(2):790-793. Available at http://www.ncbi.nlm.nih.gov/pubmed/18056284.
21. Diesenhouse MC, Wilson LA, Corrent GF, Visvesvara GS, Grossniklaus HE, Bryan RT. Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol*. Mar 15 1993;115(3):293-298. Available at http://www.ncbi.nlm.nih.gov/pubmed/8117342.
22. Dieterich DT, Lew EA, Kotler DP, Poles MA, Orenstein JM. Treatment with albendazole for intestinal disease due to *Enterocytozoon bieneusi* in patients with AIDS. *J Infect Dis*. Jan 1994;169(1):178-183. Available at http://www.ncbi.

nlm.nih.gov/pubmed/8277179.

23. Molina JM, Chastang C, Goguel J, et al. Albendazole for treatment and prophylaxis of microsporidiosis due to *Encephalitozoon intestinalis* in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis*. May 1998;177(5):1373-1377. Available at http://www.ncbi.nlm.nih.gov/pubmed/9593027.
24. Dionisio D, Manneschi LI, Di Lollo S, et al. Persistent damage to *Enterocytozoon bieneusi*, with persistent symptomatic relief, after combined furazolidone and albendazole in AIDS patients. *J Clin Pathol*. Oct 1998;51(10):731-736. Available at http://www.ncbi.nlm.nih.gov/pubmed/10023334.
25. Sriaroon C, Mayer CA, Chen L, Accurso C, Greene JN, Vincent AL. Diffuse intra-abdominal granulomatous seeding as a manifestation of immune reconstitution inflammatory syndrome associated with microsporidiosis in a patient with HIV. *AIDS Patient Care STDS*. Aug 2008;22(8):611-612. Available at http://www.ncbi.nlm.nih.gov/pubmed/18627278.
26. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med Hyg*. Dec 2008;79(6):856-863. Available at http://www.ncbi.nlm.nih.gov/pubmed/19052293.
27. Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton: Publishing Sciences Group; 1977.
28. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.
29. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.
30. Kallen B, Nilsson E, Otterblad Olausson P. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta paediatrica*. May 2008;97(5):541-545. Available at http://www.ncbi.nlm.nih.gov/pubmed/18394096.

Mycobacterium tuberculosis Infection and Disease (Last updated May 18, 2017; last reviewed May 18, 2017)

Epidemiology

Despite being preventable and curable, tuberculosis (TB) is the leading cause of death from infectious disease globally, with nearly 10 million people developing TB and 1.5 million people dying from TB in 2014.[1] TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1.2 million new HIV-infected persons reported with TB and 390,000 deaths in 2014.

TB infection occurs when a person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms. Usually within 2 to 12 weeks after infection, the immune response limits multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons with LTBI are asymptomatic and are not infectious. TB disease (defined as clinically active disease, often with positive smears and cultures) can develop soon after exposure to *M. tuberculosis* organisms (primary disease) or after reactivation of latent infection.

It is estimated that the annual risk of reactivation with TB disease among persons with untreated HIV infection is 3 to 16% per year, which approximates the lifetime risk among HIV-negative persons with LTBI (~5%).[2] TB incidence doubles in the first year following HIV infection[3] and can occur at any CD4 cell count, though the risk increases with progressive immunodeficiency.[3,4]

Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, and this effect has been documented in settings with low case rates, such as the United States,[5] and in settings with very high case rates.[6,7] However, even with the beneficial effects of ART, the risk of TB disease among persons with HIV infection remains greater than that of the general population.[8]

Rates of TB in the United States are declining, with 3.0 new cases of TB disease per 100,000 population (a total of 9,412 cases) reported in 2014, a decline of 2.2% from 2013.[9] The prevalence of LTBI in the general population of the United States is 4.7%,[10] which has remained unchanged since the last survey in 1999–2000. The incidence of HIV-related TB has declined more rapidly than the rate of active TB in the general population,[11] in part due to the widespread use of ART. In 2014, there were 506 reported cases of HIV/TB co-infection in the United States (6.3% of individuals with TB who were tested for HIV).[12] Like TB disease in the general population of the United States, HIV-related TB is increasingly a disease of persons born outside of the United States.[11] Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.[11,13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. Unlike most opportunistic infections, TB is transmissible, particularly to other persons with HIV infection. Therefore, clinicians providing care for persons with HIV must remain vigilant in efforts to prevent TB, knowledgeable about the clinical presentation of HIV-related TB, and cognizant of the complexities of the co-treatment of HIV and TB.

Preventing Exposure

In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[10] Therefore, patients with HIV infection who travel or work internationally in settings with a high prevalence of TB should be counseled about the risk of TB acquisition and the advisability of getting tested for LTBI upon return. While there are risks for TB exposure in some healthcare and correctional settings in the United States, there is no need for precautions for persons with HIV infection beyond those taken for all persons in those settings.

Preventing Disease—Diagnosis and Treatment of Latent TB Infection

The estimated annual risk for active TB among HIV-infected persons with LTBI is 3 to 12 times the risk in the general population.[14,15] Furthermore, development of HIV-related TB increases viral load,16 and the risk of HIV disease progression[16] and death,[17] compared to CD4-matched HIV-seropositive controls without TB. Risk of progression from LTBI to TB disease in HIV-infected persons is reduced both by antiretroviral treatment and by treatment of LTBI. Treatment of LTBI (as defined by a positive tuberculin skin test [TST]) decreases the risk of TB disease by 62% and the risk of death by 26% among persons with HIV infection.[18-20] Isoniazid preventive therapy and ART independently decrease the risk of death and severe HIV-related illness.[21] Among persons receiving ART, isoniazid preventive therapy further decreased the risk of TB by 37% when compared to placebo.[22] In Brazil, a country with medium TB burden, the protective effect of isoniazid against TB in HIV-infected persons with a positive TST lasted throughout 7 years of follow-up.[23] Therefore, prevention of TB disease by screening and appropriate treatment for LTBI are key components of HIV care.

Diagnosis of LTBI

All persons should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII)**. Among HIV-infected persons, the benefit of isoniazid preventive therapy has been seen primarily in persons with evidence of LTBI (e.g., a positive TST).[24,25] However, in one study in South Africa, a setting with a high TB burden, isoniazid decreased the TB risk among all persons receiving ART regardless of TST or interferon gamma release assay result.[22] Persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 cell count <200 cells/μL), and without indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be re-tested for LTBI once they start ART and attain a CD4 count ≥200 cells/μL to ensure the initial test was a true negative result.[26,27] Annual testing for LTBI using TST is recommended for HIV-infected persons who are at high risk for repeated or ongoing exposure to persons with active TB **(AIII)**.

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48 to 72 hours in HIV-infected persons) in persons with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among persons with HIV infection, the test has several disadvantages: the requirement for two visits to place and read the test, decreased specificity (false positive results) among persons who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among persons with advanced immunodeficiency.[28] These limitations of the TST have led to interest in interferon-gamma release assays (IGRA) for detection of LTBI.

Current evidence suggests that, compared to the TST, IGRAs have higher specificity (92%–97% vs. 56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*,[29] and less cross-reactivity with BCG vaccination and nontuberculous mycobacteria.[30,31] Three IGRAs are FDA-approved and available in the United States. Progressive immunodeficiency is associated with decreased sensitivity of IGRAs, though the effect of immunodeficiency on the sensitivity of IGRAs may be less than its effect on the sensitivity of the TST.[32] Like the TST, the reproducibility of positive results of IGRAs is limited.[33] Among 46 HIV-infected patients having initial positive tests with the IGRA Quantiferon-TB Gold In-Tube assay, 33 (72%) had negative repeat tests, particularly those with responses at the lower range of the manufacturer's suggested range of positive results.[34]

Among persons with HIV infection, the correlation between the TST and IGRAs is poor to moderate.[35,36] In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;[37,38] in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than were those with a positive TST.[39,40] For all of its limitations, a positive TST result remains strongly predictive of decreased risk of TB progression in response to isoniazid preventive therapy among persons with HIV infection.[18] Whether the same is true of the IGRAs remains to be demonstrated.

In programmatic settings in the United States, TB screening based on the TST has been suboptimal, with only 47% to 65% of patients completing screening.[41-43] The use of an IGRA for TB screening may increase the proportion of patients who complete TB screening.

There have been no definitive comparisons of the TST and IGRAs for screening persons with HIV infection in low-burden settings like the United States. Both the TST and the approved IGRAs are appropriate for TB screening among HIV-infected persons in the United States.[44] Some experts have suggested using both the TST and an IGRA to screen for LTBI, but the predictive value of this approach is not clear, and its adoption would be more expensive and more difficult to implement. The routine use of both TST and IGRAs to screen for LTBI **is not recommended** in the United States.[44]

As tests of immune reactivity against *M. tuberculosis*, the TST and IGRAs are often positive among persons with TB disease. Therefore, all persons with a positive TST or IGRA should be evaluated for the possibility of active TB disease. Most, but not all, HIV-infected persons with TB disease have symptoms (cough, fever, sweats, weight loss, lymphadenopathy); absence of any of these symptoms has a 97% negative predictive value for culture-positive TB, though this varies depending on pre-test probability.[45] The addition of a chest radiograph improved sensitivity of this screening algorithm, but decreased specificity. Obtaining a sputum culture is the gold standard for diagnosing pulmonary TB disease, but this is not cost-effective in screening asymptomatic HIV-infected persons, particularly in the United States where the prevalence of TB is very low. Therefore, symptom screening (asking for cough of *any* duration) coupled with chest radiography is recommended to exclude TB disease in a patient with a positive screening test.

Treatment of LTBI

Once it is established that there is no evidence of TB disease, HIV-infected persons with a positive screening test should receive prophylaxis **(AI)**. Additionally, HIV-infected close contacts of an infectious case of TB should receive prophylaxis, regardless of screening tests for LTBI. HIV-infected persons who have a negative TST and are not recent contacts of a case of infectious TB may not benefit from treatment of LTBI **(AI)**,[24,46-48] though at least one study from a high-burden setting in South Africa showed isoniazid decreased TB risk regardless of TST or IGRA result.[22]

Preferred and Alternative Drugs for LTBI Treatment, Including Duration of Therapy

Isoniazid prophylaxis for 9 months remains the preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AII)**. Although peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or various antiretroviral drugs, the risk of hepatitis—the most important of these adverse effects—is not significantly increased when isoniazid is combined with efavirenz- or nevirapine-based regimens **(BII)**.[22] Isoniazid prophylaxis should be supplemented with pyridoxine at a dose of 25 to 50 mg/day to prevent peripheral neuropathy **(AIII)**. A significant disadvantage of the 9-month regimen is that the majority of patients do not complete all 9 months of therapy.[49] Shorter regimens are more likely to be completed.[49-52] Alternative regimens for chemoprophylaxis are shown in Table 1. Rifapentine plus isoniazid given by directly observed therapy (DOT) once weekly for 12 weeks is as effective and well-tolerated as 6 to 9 months of daily LTBI treatment with isoniazid, including in persons with HIV infection whose CD4 lymphocyte counts are generally >350 cells/mm^3 and who are not yet on ART.[53-55] Although individuals taking ART were not included in the Phase 3 trial of once-weekly rifapentine and isoniazid, the pharmacokinetic (PK) profile of efavirenz with daily rifapentine is favorable.[56] In a PK study of 12 HIV-infected adults without TB receiving once-weekly 900 mg rifapentine with efavirenz, there was minimal effect on efavirenz exposure.[57] Raltegravir concentrations were modestly increased, not decreased, when it was given with once-weekly rifapentine.[58] Thus, despite the lack of clinical trial outcome data, once-weekly rifapentine/isoniazid can be used with efavirenz or raltegravir without dose adjustment based on available PK data. Increased clinical monitoring is not recommended, but should be based on clinical judgment. When using rifampin-containing regimens, either dose adjustment or substitution of key ART drugs may be needed. The regimen of two months rifampin plus pyrazinamide is not recommended due to the risk of severe and sometimes fatal hepatotoxicity **(AII)**.

LTBI treatment and ART act independently to decrease the risk of TB disease.[19,22,59,60] Therefore, use of both interventions is recommended for those persons with LTBI and an indication for ART **(AI)**.

Monitoring of Response to Treatment of LTBI

Individuals receiving self-administered daily chemoprophylaxis should be seen by the prescribing clinician on a monthly basis to assess adherence and evaluate for possible drug toxicity; generally, a clinician should not prescribe more than one month's supply of a drugs. Although HIV-infected persons may not have a higher risk of hepatitis from isoniazid prophylaxis than HIV-uninfected persons, it is recommended that baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin be measured and repeated if abnormal at baseline.[14] Persons with concomitant chronic viral hepatitis have an increased risk of isoniazid-related hepatotoxicity, and such patients should be monitored closely when treated for LTBI.[61] With isoniazid, liver enzymes typically increase in the first 3 months but then, through the process of hepatic adaptation, liver enzymes return to normal despite continued therapy. If the serum aminotransferase level increases greater than five times the upper limit of normal without symptoms or greater than three times the upper limit of normal with symptoms (or greater than two times the upper limit of normal among patients with baseline abnormal transaminases), chemoprophylaxis should be stopped. Factors that increase the risk of clinical hepatitis include daily alcohol consumption, underlying liver disease, and concurrent treatment with other hepatotoxic drugs. Patients should be reminded at each visit about potential adverse effects (unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, and arthralgia) and told to immediately stop isoniazid and return to the clinic for an assessment should any of these occur.

The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease[62] and in consultation with an expert in treating LTBI in persons with HIV infection.

Clinical Manifestations of TB Disease

The presence of any one of the classic symptoms of TB disease (cough, fever, night sweats, and weight loss) has high sensitivity but low specificity for diagnosing TB.[45] The sensitivity of classic TB symptoms is lower in people on ART.[63] Culture-positive TB disease can be subclinical or oligo-symptomatic.[64] The duration of symptoms is shorter in HIV-infected patients,[65] and in patients who are markedly immune suppressed TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.[66] After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection (see section below on "Unmasking TB-IRIS").

The presentation of active TB disease is influenced by the degree of immunodeficiency.[67,68] In HIV-infected patients with CD4 counts >200 cells/μL, HIV-related TB generally resembles TB among HIV-uninfected persons. The majority of patients have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.[69]

In patients with CD4 counts <200 cells/μL, the chest radiographic findings of pulmonary TB are markedly different with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon.[67,69,70] Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures.[71]

With increasing degrees of immunodeficiency, extrapulmonary or disseminated TB (e.g., lymphadenitis, genitourinary TB, osteal TB, pleuritis, pericarditis, and meningitis), with or without pulmonary involvement, are more common. Clinical manifestations of extrapulmonary TB are not substantially different from those described in HIV-uninfected persons. TB must be considered in disease processes involving any site in the body,[72] but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.[73-75]

Diagnosis

Initial diagnostic testing is directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid). The initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph, even in the absence of pulmonary symptoms or signs; pulmonary involvement is common at all CD4 counts.[64,76] However, chest radiography is an imperfect screen for pulmonary TB, particularly among patients with advanced immunodeficiency who can have TB culture positive sputum despite normal chest radiographs.[77,78] Therefore, sputum smear and culture should be considered in symptomatic patients being evaluated for possible TB disease who have a normal chest radiograph as well as in persons with no pulmonary symptoms but evidence of TB disease elsewhere.

Sputum smear-negative TB is common among persons with HIV infection, particularly those with advanced immunodeficiency and non-cavitary disease.[79] However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. If a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high.[80] Smear and culture of three sputum specimens is recommended in that there was a 10% incremental yield for broth culture between the second and third specimens in a recent large study of patients with HIV.[81]

Extrapulmonary and disseminated TB are more common in persons with HIV infection, particularly with advanced immunosuppression.[82,83] Nodal involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.[84] Histopathologic findings also are affected by the degree of immunodeficiency. Persons with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent.[68]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. The yield of acid-fast bacilli (AFB) smear, culture, and nucleic acid amplification (NAA) testing is generally lower from extrapulmonary specimens compared to sputum but nonetheless can be an important diagnostic tool when *M. tuberculosis* is isolated. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among patients with advanced immunodeficiency, the yield of culture from these two readily-available body fluids can be relatively high[68,72] and may allow definitive diagnosis and be a source of an isolate for drug-susceptibility testing.

Nucleic-acid amplification testing: Standard mycobacterial cultures for TB may take weeks to months to grow, but rapid diagnosis is needed in patients with HIV infection given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB (some assays also provide rapid detection of drug resistance—see below). NAA tests have at least two uses among patients with suspected HIV-related TB. First, these assays are highly predictive of TB among specimens that are AFB smear-positive. Non-tuberculous mycobacterial infections are relatively common among patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation among patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, being positive in 50 to 80% of smear-negative, culture-positive specimens[85,86] and up to 90% when three NAA tests are performed. Therefore, use of an NAA test is recommended on at least one specimen from all patients with suspected pulmonary TB.[87] NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than in sputum specimens.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations associated with rifampin resistance. It has been widely implemented in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in HIV-infected patients.[88] Xpert MTB/RIF was licensed in the United States in 2013 for detection of *M. tuberculosis* and reporting of rifampin resistance directly from sputum samples[89] and as an aid in decisions regarding respiratory isolation in 2015.[90] This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a recent meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were

88% (95% confidence interval 83%–92%) and 98% (95% confidence interval 97%–99%), respectively. The assay is somewhat less sensitive among HIV-infected patients (pooled sensitivity of 80%, 95% confidence interval 67%–88%) than among HIV-uninfected patients (pooled sensitivity of 89%, 95% confidence interval 81%–94%);[91] however, this may be in part attributed to a higher prevalence of smear negative disease in HIV-infected individuals.[92] In some studies, the sensitivity of Xpert MTB/RIF has been related to CD4 cell count, with higher sensitivity among patients with more advanced immunodeficiency.[93]

In extrapulmonary specimens, a 2014 meta-analysis reported Xpert MTB/RIF sensitivity of up to 95% in smear positive specimens and 69% in smear negative specimens.[94] Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), CSF (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%).

Lipoarabinomannan (LAM): LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of TB patients. LAM can be detected using an ELISA or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity but has the advantages of being available as a true point of care test that can be performed on urine. LAM has demonstrated the best performance in HIV-infected patients with low CD4 cell counts (<100 cells/mm^3) with a sensitivity of 37 to 56% and specificity of up to 95%.[95-97] In addition, LAM has higher sensitivity in patients with worse prognoses,[98] who are therefore a high priority to identify. Combining LAM with other diagnostic strategies such as Xpert MTB/RIF testing or smear may improve the diagnostic utility.[99,100]

Immune-based tests: Immunological tests for TB infection, the TST and IGRA, may be helpful in unusual circumstances in which it is difficult to obtain definitive culture evidence for active TB; evidence of prior TB infection increases the likelihood that a clinical illness may be TB disease. However, these tests are not diagnostic of active TB, and a negative TST or IGRA should never be interpreted as ruling out TB disease because TB may cause anergy and these tests may be negative in up to 11 to 30% of patients with active TB.[44]

Drug susceptibility testing: Drug-susceptibility testing should be performed on the initial isolates for all patients suspected of having TB, as resistance to isoniazid and/or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[101] The presence of multidrug-resistant TB (MDR TB; defined as resistance to at least isoniazid and rifampin) or extensively drug-resistant TB (XDR TB; defined as MDR TB with additional resistance to a fluoroquinolone and either kanamycin, amikacin, or capreomycin) is associated with a markedly increased risk of death.[102] Thus, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.

For all patients with TB disease, drug-susceptibility testing to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. Drug-susceptibility tests (DST) should be repeated if sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive 1 month or longer after culture conversion to negative. DST for second-line TB medications (fluoroquinolones, aminoglycosides, capreomycin, ethionamide, and others) should be performed only in reference laboratories with substantial experience in these techniques and should be limited to specimens with resistance to first-line TB medications.

Phenotypic drug-susceptibility testing: Conventional DST is widely used, and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turn-around time of conventional broth or agar-based culture followed by DST may be as long as 6 weeks,[103] due to the slow growth of *M. tuberculosis*. During this time, patients with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow for ongoing transmission, further clinical deterioration, and death, particularly in HIV-infected individuals.[102]

NAA testing for drug resistance: Genotypic testing to identify mutations that confer drug resistance allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied

for a number of TB medications.[104] Commercial NAA tests such as Xpert MTB/RIF identify resistance mutations associated with rifampin and commercially available line probe assays identify genotypic resistance for rifampin and isoniazid.[92,105] Next generation commercial line probe assays such as GenoType MTBDR*sl* identify genotypic resistance to other TB medications, but results should be confirmed with standard culture-based DST.[106] Several assays can be performed on cultured isolates or directly on sputum specimens.

The largest clinical experience with rapid molecular tests for rifampin resistance is with the Xpert MTB/RIF assay. In a 2014 meta-analysis, the sensitivity for detection of rifampin resistance was 95% (95% confidence interval 90%–97%) and specificity was 98% (95% confidence interval 97%–99%).[91] False-positive results for rifampin resistance with the Xpert MTB/RIF assay can occur, although this appears to be less common with the current version of the assay.[107] However, the comparator for most studies—phenotypic drug-susceptibility testing—should not be considered an absolute gold standard.[108,109] Some isolates with rifampin resistance by the Xpert MTB/RIF assay have mutations in the *rpoB* gene, but are susceptible in phenotypic assays. Two recent analyses showed that treatment failure was more common among patients whose isolates had phenotypic susceptibility but mutations in the *rpoB* gene compared to patients whose isolates had normal *rpoB* gene sequences.[110,111]

In low MDR TB prevalence settings such as the United States, the positive predictive value of any test for rifampin resistance is limited. Therefore, isolates with an initial reading of rifampin resistance with the Xpert MTB/RIF should undergo confirmatory testing (*rpoB* gene sequencing, phenotypic drug susceptibility testing), and additional specimens should be obtained from such patients. Consultation with an expert in the diagnosis and treatment of MDR TB should be strongly considered.

Clinicians who suspect drug-resistant TB in an HIV-infected patient should make every effort to expedite their diagnosis. In the United States, the Centers for Disease Control and Prevention (CDC), Division of TB Elimination, has a Molecular Detection of Drug Resistance (MDDR) service to make rapid molecular testing for first-and second-line TB medications available for persons suspected of having drug-resistant TB (http://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/moldstreport.pdf).

Drug resistance should be considered in any patient with:

- known exposure to a drug-resistant TB case
- residence in a setting with high rates of primary drug-resistant TB (e.g., a country or area with high rates of drug-resistant TB in new patients)
- persistently positive smear or culture results at or after 4 months of treatment
- previous TB treatment, particularly if it was not directly observed or was interrupted for any reason

Treatment of Disease

Preferred and Alternative Drugs for Treatment, Including Duration of Therapy

TB among persons with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens.[80] Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is warranted in patients with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.

Treatment of suspected TB for HIV-infected individuals is the same as for HIV-uninfected persons, and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI)**. If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen—including a fluoroquinolone (levofloxacin or moxifloxacin) and either an aminoglycoside or capreomycin—should be used **(BIII)** and can be adjusted once complete DST results are available. DOT is recommended for all patients with suspected HIV-related TB **(AII)**. The likelihood of treatment success is further enhanced with comprehensive case management, assistance with housing and other social support,

and assistance in establishing or re-engaging with HIV care, if needed (enhanced DOT).

Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs listed above. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy, generally recommended as an additional 4 months of treatment for uncomplicated TB **(AI)**.

Although intermittent dosing (administration less often than daily) of anti-TB treatment facilitates DOT, regimens that included twice- or thrice-weekly dosing during the intensive phase have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in HIV co-infected persons.[112-117] Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive treatment phase **(AII)**. Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were also associated with increased risks of treatment failure or relapse with acquired rifamycin resistance.[118,119] Therefore, daily (5–7 days per week) dosing is also recommended during the continuation phase of therapy **(AII)**. Although drug-drug interaction studies suggest that thrice-weekly and daily rifampin dosing is associated with similar levels of cytochrome P450 enzyme induction when dosed with raltegravir,[120] whether there is a difference between daily and thrice-weekly dosing during the continuation phase of therapy has not been adequately studied in randomized trials. Observational studies and meta-analyses focused primarily on the intensive phase of treatment and thrice-weekly therapy during the continuation phase was not systematically evaluated in the context of the risk of adverse TB outcomes (treatment failure, recurrence, or acquired drug resistance).[115] Although earlier recommendations for TB treatment in HIV-uninfected persons indicated that therapy should be based on the number of doses received rather than the duration of therapy, there are no data substantiating the minimum number of doses needed within a specified time interval in HIV-infected individuals. Every effort should be made to assure that patients receive daily therapy as previously described, allowing up to 28 weeks to complete at least 24 weeks (6 months) of treatment to accommodate brief interruptions of therapy for management of adverse drug reactions as described below.

The optimal duration of TB treatment for patients with HIV infection and drug-susceptible TB disease is not known. In general, the outcomes of 6-month regimens (2 months of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV co-infection have been good.[1,12] A randomized trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy, but the trial was underpowered.[121] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy, compared to those assigned to 9-[112] or 12-month regimens.[122] However, the applicability of these two trials is uncertain in low-burden settings in which ART is used, such as the United States.

Three randomized clinical trials have evaluated strategies to reduce the duration of anti-TB treatment from 6 to 4 months in persons with drug-susceptible TB by substituting moxifloxacin or gatifloxacin for either ethambutol or isoniazid in the intensive phase of treatment and adding one of these to a 2-month continuation phase.[123-125] A fourth study evaluated the substitution of moxifloxacin for ethambutol and the substitution of rifapentine for rifampin in a 4-month regimen.[126] In each of these trials, despite evidence of more rapid sputum culture conversion, overall 2-month culture conversion rates were not significantly different than with the standard 6-month control regimen, and rates of unfavorable outcomes (as defined by treatment failure or relapse after 18 months of follow-up) were higher. The number of HIV-infected participants in these studies was small, but when analyzed by HIV status the results were similar. These findings reinforce the current recommendation to treat drug-susceptible TB in HIV-infected individuals for at least 6 months **(BII)**. Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture **(BII)**.

Intensified therapy for CNS TB may be beneficial, but there are limited data to support this. A recent randomized trial that compared 9 months of standard therapy that included rifampicin at a dose of 10 mg/kg with an intensified regimen in which levofloxacin was added and rifampicin was given at a higher dose of 15 mg/kg showed similar rates of survival, adverse events, and secondary outcomes in both HIV-uninfected

and HIV co-infected individuals with tuberculous meningitis.[127] A PK study of 60 participants in Indonesia suggested that rifampicin administered in doses equivalent to 13 mg/kg or higher given intravenously (similar to 26 mg/kg delivered orally) reduced mortality,[128] but this finding requires confirmation in a larger trial. Addition of a fluoroquinolone may improve outcomes in patients with isoniazid-monoresistant tuberculous meningitis.[127]

Adjunctive corticosteroid therapy should be considered in HIV-infected individuals with TB involving the CNS or pericardium **(AI)**.[129] Adjunctive corticosteroid therapy increases survival overall for patients with TB and CNS involvement, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV infection.[75] Adjunctive corticosteroid therapy reduces the incidence of constrictive pericarditis, although in a randomized trial of adjunctive prednisolone compared with placebo administered for 6 weeks in HIV-uninfected and co-infected individuals with tuberculous pericarditis, prednisolone was not associated with a significant reduction in the composite endpoint of death, cardiac tamponade, or constrictive pericarditis. Those receiving prednisolone also had a higher incidence of some cancers.[129] There have been no trials comparing different doses and treatment durations of adjunctive corticosteroids. Dexamethasone was used in trials of adjunctive corticosteroids for CNS disease (0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks); prednisone or prednisolone was used in trials of pericardial disease (60 mg/day and taper 10 mg per week; total duration of 6 weeks).[75,129]

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed. Although data are conflicting with regard to whether sequential treatment of TB followed by initiation of ART is acceptable for those with CD4 cell counts >220 to 250 cells/mm^3,[130,131] recently published results from large, international, randomized trials of immediate versus delayed initiation of ART indicate that substantial personal health benefits accrue at all CD4 cell counts in persons without active TB. When coupled with the preponderance of data from randomized trials in persons with HIV and active TB, these results support the recommendation that ART should not be withheld until completion of TB treatment **(AI)**.[21,132,133] Co-treatment of HIV and TB is complex because of the adherence demands of multidrug therapy for two infections, drug-drug interactions between the rifamycins and many antiretroviral drugs, overlapping side effect profiles of anti-TB and antiretroviral drugs, and the development of immune reconstitution inflammatory syndrome (IRIS), although the rates of IRIS are higher primarily in those with lower CD4 cell counts. Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival[130] (particularly for persons with CD4 cell counts <50 cells/μL), decreases the risk of additional opportunistic illnesses,[134] can achieve high rates of viral suppression,[135] may improve TB treatment outcomes,[136] and, despite higher rates of IRIS at low CD4 cell counts, is not associated with higher rates of other treatment-related adverse events.[131]

The SAPIT trial randomized 642 South African adults with CD4 cell counts <500 cells/mm^3 and AFB smear + TB to start ART at TB treatment initiation, after the intensive phase of TB therapy but before TB treatment completion, or after TB treatment completion.[130] The study was stopped early when the mortality of the two integrated treatment arms was 56% lower than the sequential treatment arm, demonstrating that ART should be started before TB completion. Notably, there was a survival benefit across the range of CD4 cell counts among patients enrolled, including within the stratum of baseline CD4 cell counts from 200 to 500/mm^3.

The CAMELIA, STRIDE (ACTG A5221), and TB-HAART trials shed further light on the optimal timing of ART during the course of TB treatment. In CAMELIA, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 cell count of 25 cells/mm^3 (IQR, 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality was decreased from 13% in the 2-week arm to 8% in the 8-week arm,[137] and viral suppression rates were very high among those who survived (>95%).

The ACTG A5221 STRIDE study randomized 809 patients from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 cell count of 77 cells/mm^3 (IQR, 33,146)

to immediate ART (within 2 weeks) or early ART (8–12 weeks).[138] A new OI or death occurred among 12.9% of patients in the immediate arm and 16.1% in the early arm by week 48 ($P = 0.45$). In patients with screening CD4 lymphocytes <50 cells/mm^3, 15.5% of patients on the immediate arm versus 26.6% on early ART experienced AIDS or death, ($P = 0.02$). Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) was more common in the immediate ART arm (11%) compared to the early arm (5%), $P = 0.002$. Viral suppression rates were similar between the arms.

The TB-HAART trial included 1,538 HIV-infected patients in South Africa, Uganda, Zambia, and Tanzania who had culture-confirmed pulmonary TB and CD4 cell counts ≥220 cells/mm^3 and who had tolerated 2 weeks of TB treatment. Subjects were randomized to early (after 2 weeks of TB treatment initiation) versus delayed (until 6 months after initiation of TB treatment) ART.[131] The median CD4 cell count overall was 367 cells/mm^3 (IQR 289, 456). The composite primary endpoint of TB treatment failure, recurrence and death within 12 months of starting TB treatment occurred in 8.5% of patients in the early ART group and 9.2% in the delayed group (RR 0.91, 95% CI 0.64-1.30; $P = 0.9$). Mortality, grade 3 and 4 adverse events and IRIS did not differ among the treatment groups. Patients in the early ART group had higher CD4 cell counts at all time points than those in the delayed ART group; no data on viral suppression were available. Unlike SAPIT, STRIDE, and CAMELIA, the TB-HAART study concluded that ART can be delayed until after 6 months of TB treatment for patients with CD4 cell counts >220 cells/mm^3.

The optimal approach for initiation of ART in TB meningitis remains uncertain. A randomized trial conducted in Vietnam compared ART initiation immediately (within 7 days of starting TB treatment) or 2 months after starting TB treatment among 253 patients with HIV-related TB meningitis.[139] This study did not show a survival benefit to early ART initiation. On the contrary, early ART was associated with similar mortality and more frequent and severe adverse events (86%) compared to the deferred ART arm (75%). The overall mortality rates in this study were very high (58%), likely at least in part because the majority of participants had advanced AIDS (median baseline CD4 cell count 41 cells/mm^3); it is unclear if these findings would generalize to other settings. Nonetheless, caution in the timing of ART initiation with specific monitoring for drug-related toxicities is warranted in patients with TB disease affecting the CNS.

In conclusion, ART is recommended in all HIV-infected persons with TB **(AI)**. For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation when the CD4 cell count is <50 cells/mm^3 and, based on the preponderance of data, within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts **(AI)**. Given the need for the initiation of five to seven new medications in a short time, adherence support should be offered. In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk for severe adverse effects, and an expert should be consulted and careful monitoring provided. Early ART initiation requires close collaboration between HIV and TB care clinics, expertise in management of ART regimen selection, and support and adherence services for clients.

When TB occurs in patients already on ART, treatment for TB must be started immediately **(AIII)**, and ART should be modified to reduce the risk for drug interactions and maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug resistance testing should be performed and intensified adherence counseling should be provided. A new ART regimen may be required to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

Drug-Drug Interactions in the Treatment of HIV-Related TB

The rifamycin class of antibiotics is the key to effective, short-course treatment for drug-sensitive TB. However, the currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with a number of antiretroviral drugs (Table 3 [TB Drug Dosing] and the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). These drug-drug interactions are complex, but most result from the potent induction by the rifamycin of genes involved in the metabolism and transport of antiretroviral agents.

The preferred co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an

antiretroviral regimen of efavirenz plus two nucleoside(tide) analogues **(AII)**. Efavirenz-based ART is associated with excellent TB and HIV treatment outcomes and has low rates of serious toxicity.[140] Data on the magnitude of the change in efavirenz concentrations when co-administered with rifampin are conflicting. Early studies reported a 26% reduction in efavirenz plasma concentrations,[141] but more recent and larger studies in HIV-infected patients with TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations in the majority of patients.[142-144] Previous recommendations to increase the dose of efavirenz, especially in patients weighing >60 kg, are thus not supported by good data and have several disadvantages (complexity of dosing, inability to take advantage of the simplicity of the co-formulation of efavirenz, tenofovir disoproxil fumarate, and emtricitabine, and the possibility of increased neuropsychiatric side effects). Given the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[140,145] the 600 mg daily dose of efavirenz is recommended **(BII)**.

Rifampin has a more significant effect on the concentration of nevirapine. Earlier studies suggested that clinical outcomes were reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an antiretroviral regimen of nevirapine plus two nucleoside analogues when nevirapine once-daily lead-in dosing was avoided.[140,146-148] However, more recent data and a meta-analysis indicate that co-treatment with nevirapine-based ART is associated with less satisfactory virologic outcomes and increased incidence of drug discontinuation due to adverse events than efavirenz-based ART in patients on TB treatment.[149-151] Nevirapine should generally be avoided unless there are no other options **(AI)**. For patients unable to take efavirenz due to intolerance, nevirapine-based ART is a reasonable alternative, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin.[140]

Alternatives to efavirenz-based antiretroviral treatment for HIV/TB co-infected patients include regimens with integrase inhibitors or protease inhibitors (PIs). One preferred alternative co-treatment regimen is the combination of raltegravir-based antiretroviral treatment, using 400 or 800 mg twice daily, with standard rifampin dosing **(BI)**.[152] Another alternative co-treatment regimen is rifabutin-based TB therapy with an antiretroviral regimen including a ritonavir-boosted PI **(BIII)**. While there are no clinical trials specifically comparing rifampin and rifabutin-containing anti-TB regimens among persons with HIV/TB co-infection taking ART, in general, rifabutin is thought to be a reasonable substitute for rifampin for treatment of TB.[153,154] Although the dramatic effects of rifampin on serum concentrations of lopinavir may be overcome by doubling the dose of lopinavir/ritonavir,[155,156] the safety of this strategy has yet to be firmly established. High rates of hepatotoxicity were reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[157-159] In patients with HIV and TB co-infection, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampicin-based TB treatment, but the strategy of increasing ritonavir dosing to 400 mg twice daily leads to high rates of hepatotoxicity.[156,160,161] Thus, a strategy of first increasing the dose by 50%, then increasing to full double dose is recommended **(BIII)**. Regular monitoring of transaminases is recommended when double dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once stable on full dose).

Use of rifabutin with boosted PI is thus preferred to use of rifampin with double-dose PI in settings where rifabutin is readily available. Rifabutin has little effect on ritonavir-boosted lopinavir[162] or atazanavir,[163] and its co-administration results in moderate increases in darunavir[164] and fosamprenavir concentrations.[165] However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal metabolites, desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased to avoid dose-related toxicity, such as uveitis and neutropenia.[166] In studies of HIV-infected people, rifabutin exposures were significantly lower when rifabutin was dosed 150 mg thrice-weekly with lopinavir/ritonavir compared with rifabutin concentrations when given 300 mg daily in the absence of a protease inhibitor, but concentrations of the active desacetyl metabolite were high.[167,168] Among individuals co-infected with HIV and TB, there have been case reports of acquired rifamycin resistance with 150 mg thrice-weekly doses of rifabutin in the presence of a boosted PI-based antiretroviral regimen.[169,170] A recent study conducted in South Africa in 16 HIV-infected patients on a lopinavir/ritonavir-based ART regimen demonstrated that rifabutin administered in a dose of 150 mg daily in combination with

lopinavir/ritonavir was generally safe and associated with rifabutin plasma concentrations similar to those shown to prevent acquired rifamycin resistance (i.e., rifabutin given 300 mg daily in the absence of a boosted PI).[168] A randomized clinical trial evaluating rifabutin PK and TB and ART outcomes using this dose with lopinavir/ritonavir-based ART is in progress. Based on available PK data, it is recommended that rifabutin should be dosed 150 mg daily (at least during the first 2 months of TB treatment) in patients who are on a ritonavir-boosted PI-containing antiretroviral regimen **(BII)**. However, given that the risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy has not been firmly established, close monitoring for toxicity (especially neutropenia and uveitis) is required until larger studies provide adequate safety data. Close monitoring of adherence to ART is essential as these reduced doses of rifabutin would be inadequate if the patient stopped taking the PI, putting the patient at risk of rifamycin-resistant TB.

Raltegravir concentrations are significantly decreased when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[171] However, it is unclear whether or not an increase in dose is needed. In a Phase 2 randomized trial in HIV-infected people with TB, virologic responses appeared to be similar in non-comparative analyses of the raltegravir 400 and 800 mg twice daily arms.[152] Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without dose adjustment of either drug.[172] Dolutegravir may be another reasonable treatment option. A pharmacokinetic study in healthy volunteers showed that increasing the dose of dolutegravir to 50 mg twice a day with rifampin resulted in similar exposure to dolutegravir dosed 50 mg daily without rifampin, and that rifabutin 300 mg daily did not significantly reduce the area under the concentration curve of dolutegravir.[173] Dolutegravir has not yet been studied in a significant number of HIV-infected individuals with TB. Due to the potential for significant drug interactions as detailed above, the following drugs should not be used with rifampin: rilpivirine, etravirine, tenofovir alafenamide and elvitegravir co-formulated with cobicistat **(AIII)**. Their use with rifabutin has not been evaluated.

The breadth and magnitude of drug-drug interactions between the rifamycins and many antiretroviral drugs can be daunting. Nevertheless, every effort should be made to include a rifamycin in the TB treatment regimen; the drug-drug interactions between rifamycins and antiretroviral drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included just 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among patients with HIV-related TB.[174,175] If a rifamycin cannot be used, TB treatment duration must be extended substantially, as there is currently no drug substitute with the curative power of rifampin. Thus, patients with rifamycin-susceptible *M. tuberculosis* isolates should only be treated with a regimen that does not contain a rifamycin when the patient has had a serious adverse event that is highly likely to be due to a rifamycin **(AIII)**.

Monitoring the Response to Therapy

Patients with pulmonary TB should have monthly sputum smears and cultures performed to document culture conversion on therapy (defined as two consecutive negative cultures). Patients with susceptible TB typically convert sputum cultures to negative by 2 months of first-line TB therapy, although patients with advanced disease (i.e., cavitary TB disease) may take longer to convert sputum cultures to negative.[176] Patients who have not had sputum culture conversion at or after 4 months of therapy have failed treatment and should have sputum sent for resistance testing.

Management of Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate regimen prescribed, subtherapeutic drug levels due to malabsorption, super-infection with drug-resistant *M. tuberculosis*, and acquired drug-resistance.

Patients with suspected treatment failure should be evaluated with a history, physical exam, and chest radiograph to determine whether the patient has clinically responded to therapy, even though his/her cultures have not converted. The initial culture results and drug-resistance tests, treatment regimen, and adherence should also be reviewed. Samples from all available sites (e.g., sputum, blood, urine, etc.) should be taken

for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or super-infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, empiric TB treatment should be broadened using second-line TB drugs, in consultation with an expert in the field **(BIII)**.

Adverse Drug Reactions in TB Patients on ART

HIV-infected patients not on ART are more likely to experience adverse events thought to be drug-related during the course of anti-TB therapy than HIV-uninfected patients.[177,178] Many adverse drug reactions are shared between antiretrovirals and anti-TB therapy, including the potentially life-threatening drug-induced liver injury (DILI) and cutaneous adverse drug reactions (CADRs). Retrospective observational studies had reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy,[177] but two recent randomized controlled trials of ART commencement during or after anti-TB therapy reported similar rates of adverse events during anti-TB therapy with and without ART.[130,131] Therefore, there does not seem to be significant additive toxicity when ART is given together with anti-TB therapy. However, managing suspected adverse drug reactions in this setting is complex, because assigning causality to individual drugs in patients on anti-TB drugs, ART, and cotrimoxazole is very difficult.

Because alternative drugs are less efficacious and have more toxicities than first-line anti-TB drugs, the first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently without strong evidence that the specific anti-TB drug was the cause of the reaction. In such situations, decisions regarding re-challenge with first-line drugs and/or substitution of second-line drugs should be made in consultation with a specialist in treating TB disease in persons with HIV infection.

DILI can be caused by isoniazid, rifamycins, pyrazinamide, many antiretroviral drugs, and cotrimoxazole. Anti-TB DILI is defined as an ALT elevation to ≥3 times the upper limit of normal (ULN) in the presence of symptoms (e.g., fever, rash, fatigue, nausea, anorexia, jaundice), or ≥5 times the ULN in the absence of symptoms. An increase in ALT concentration occurs in approximately 5 to 30% of patients treated with the standard four-drug anti-TB regimen,[62,179] but many of these patients only have transient, mild elevations of ALT.[62] If these criteria are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately. Serologic testing for hepatitis A, B, and C should be performed, and the patient should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins. At least three anti-TB drugs should be started (ethambutol, an aminoglycoside, and moxifloxacin or levofloxacin[180]) as a "bridging regimen" until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII)**. A re-challenge with the hepatotoxic first-line anti-TB medications can be started by adding them one at a time at intervals of 7 days to the "bridging regimen" after the ALT level returns to <2.5 times the ULN (or to near baseline for patients with pre-existing abnormalities) with frequent monitoring of ALT. Re-challenge was successful in almost 90% of HIV-uninfected patients in one randomized controlled trial of different re-challenge regimens.[180] Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Re-challenge with pyrazinamide is controversial, because some studies have reported high rates of recurrent ALT elevations, but this may be considered in severe forms of TB (e.g., meningitis or disseminated TB).[181] Depending on the outcome of the re-challenge, the anti-TB therapy regimen and duration may need to be altered—expert consultation is advised. After anti-TB drug re-challenge, if appropriate, relevant antiretroviral drugs and cotrimoxazole may be restarted.

CADRs may occur with all of the first-line anti-TB drugs, notably rifampin and isoniazid,[182] many antiretroviral drugs, notably the non-nucleoside reverse transcriptase inhibitors, and cotrimoxazole. If rash is minor, affects a limited area, and causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications continued. If the rash is generalized, or associated with fever or DILI, or if there is mucous membrane involvement or desquamation, all anti-TB medications, relevant antiretrovirals, and cotrimoxazole should be stopped. When the rash is substantially improved, the TB drug should be

restarted as described in the section on DILI above. If the rash recurs, the last drug that had been added should be stopped and the TB regimen modified. Thereafter, if appropriate, relevant antiretroviral drugs and cotrimoxazole may be recommenced.

Management of Drug-Resistant TB

Although drug-resistant TB represents a small fraction of TB cases seen in the United States, the increasing prevalence of drug-resistant TB globally, plus the high proportion of TB cases in the United States in people who are foreign-born, make it increasingly likely that local TB programs will be faced with this complex disease. There is a need for clinical trials to determine the optimal management of patients with drug-resistant TB. The most active and effective TB drugs are those used in first-line TB treatment regimens (isoniazid and rifampin, in particular). When resistance develops to these medications, alternative combinations of first- and second-line TB medications must be used, but their optimal use has not been tested using rigorous clinical trials.

Growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid monoresistance,[183] particularly in patients with HIV co-infection.[112] Substitution of a fluoroquinolone (levofloxacin or moxifloxacin) for isoniazid is suggested for at least the first 2 months of therapy **(BIII)** and considered during the continuation phase with rifampin and ethambutol as well **(CIII)**, for a total duration of treatment of 9 months **(BII)**.

Resistance to rifampin alone, or to rifampin and other drugs, substantially increases the complexity and duration of treatment. Treatment of these drug-resistant TB cases requires the use of second-line and often third-line TB medications, which are less effective, more toxic, and require 12 to 24 months of treatment (ATS/CDC/IDSA 2003).[184] Treatment outcomes for MDR TB are considerably worse than those for drug-susceptible TB—especially in patients with HIV co-infection.[102] Consensus treatment guidelines for MDR TB[184] are based on a review of published observational studies[185] and recommend use of at least five drugs with known or likely activity against the patient's isolate **(BIII)**. In general, such regimens will include a later-generation fluoroquinolone, a second-line injectable agent (i.e., kanamycin, amikacin, or capreomycin), ethionamide, pyrazinamide and at least one other second-line drug, such as cycloserine or para-aminosalicylic acid **(BIII)**. Additional resistance to one or more of these drugs (e.g., extensively drug-resistant [XDR] TB), however, may necessitate use of alternate or third-line agents with uncertain anti-TB activity. Whenever possible, treatment should be individualized to the patient's specific drug-susceptibility testing results or based upon his or her treatment history. An intensive phase of 8 months is then followed by a continuation phase without the injectable agent for an additional 12 to 18 months. Surgery (removal of the TB lesion) should be considered as an adjunctive measure in those with localized disease.[186]

The World Health Organization (WHO) recently issued guidance for programs in resource-limited settings on a standardized shorter-course regimen that includes seven anti-TB drugs and a duration of 9 to 12 months of treatment for selected patients with MDR TB.[187] The regimen composition is based on combinations evaluated as the Bangladesh regimen,[188] and includes kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol administered for 4 to 6 months, followed by moxifloxacin, clofazimine, pyrazinamide and ethambutol for 5 months. This approach has not been evaluated in randomized clinical trials among HIV-infected persons on ART or in higher resourced settings with consistent access to DST such as the United States. Based on promising observational data, an additional clinical trial is examining the efficacy of an intensive, shortened, 9-month treatment regimen for MDR TB (NCT02409290) using currently available medications, but at present there are insufficient data to support this approach in HIV-infected individuals.

Current medications for MDR TB carry considerable toxicity, including irreversible hearing loss, hypothyroidism, psychosis, and treatment-limiting gastrointestinal discomfort. Given the prolonged treatment course for MDR TB (20–24 months), patients and family members must be counseled ahead of time about possible side effects and educated regarding the importance of treatment adherence. While on therapy,

patients should be monitored closely for the appearance of side effects. Such screening should include serum chemistries, liver function tests, thyroid stimulating hormone, and audiometry. Sputum cultures should be sent monthly, even after culture-conversion, so that any relapse and amplified resistance are detected early.

The treatment of MDR TB is evolving as new drugs for TB treatment are introduced. Bedaquiline, a novel drug in an entirely new class, was recently approved in the United States for treatment of MDR TB. However, late, unexplained higher mortality among the relatively small number of patients who received bedaquiline in randomized trials[189] suggests that this drug should be used with caution and only in patients without other MDR TB treatment options while awaiting additional studies.[190] Although clinical experience with bedaquiline is still very limited, early studies have revealed several important drug-drug interactions with common antiretroviral agents. Specifically, efavirenz decreases bedaquiline levels and should not be used concurrently.[173] Lopinavir/ritonavir, by contrast, increases bedaquiline plasma concentrations approximately 2-fold when given at steady-state, but the clinical significance of this increase is not yet known.[191,192]

Delamanid, an additional new agent with a mechanism of action distinct from bedaquiline's, has also shown promise in early phase clinical trials.[193] Delamanid has been approved in Europe and Japan but is not yet available in the United States. A Phase 3 trial is currently underway (NCT01424670).

Given these complexities, treatment of MDR TB should involve an expert with experience in treating drug-resistant TB cases (one option is to contact a CDC Regional Training and Medical Consultation Center at http://www.cdc.gov/tb/education/rtmc/default.htm, if a local expert is not available).

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

TB-IRIS is a frequent early complication of ART in patients with recently diagnosed or undiagnosed active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[194-196] TB-IRIS is characterized by excessive local or systemic inflammation. Two forms of TB-IRIS are recognized: paradoxical TB-IRIS and unmasking TB-IRIS. Proposed clinical case definitions for these syndromes have been published.[197]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB prior to starting ART. Typically, these patients have had clinical improvement on TB treatment prior to starting ART. Within the first weeks of ART (though sometimes later), they develop new or recurrent symptoms as well as new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include hectic fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,[195,198] but life-threatening manifestations include enlarging cerebral tuberculomas, meningitis, enlargement of pericardial effusions causing cardiac tamponade, extensive pulmonary involvement with respiratory failure, nodal enlargement causing airway obstruction, and splenic rupture due to rapid enlargement.[195,199,200] In patients with disseminated TB, hepatic TB-IRIS is common. This manifests with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[201,202] A liver biopsy reveals a granulomatous hepatitis.[203] Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common among patients starting ART while on TB treatment (incidence 48%–54%). A recent meta-analysis provided a pooled incidence of 18%, with death attributable to TB-IRIS occurring in 2% of TB-IRIS cases.[204] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[205-210] The syndrome lasts for 2 to 3 months on average,[199,211] but some cases may have symptoms for months and rarely local manifestations may persist or recur over a year after onset.[197,211,212] Such prolonged TB-IRIS cases usually manifest with suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 cell count at start of ART, especially those patients with a CD4 cell count <100 cells/mm^3,[208,213] high HIV viral load prior to

ART,[214,215] disseminated or extrapulmonary TB,[199,207,209,213] and a short interval between starting TB treatment and ART, particularly if ART is started within the first 1 to 2 months of TB treatment.[199,206,208] Even though early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in those with CD4 cell counts <50 cells/μL, given that this reduces risk of AIDS progression and death.[204]

The diagnosis of paradoxical TB-IRIS may be challenging and there is no definitive confirmatory test. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms prior to ART, deterioration with inflammatory features of TB soon after starting ART, demonstration of a response to ART (CD4 rise and/or HIV viral load reduction) and, very importantly, investigations to exclude alternative causes for deterioration, particularly undetected TB drug resistance.[202]

Management of Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many patients require symptomatic therapy (analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy should be considered. One randomized, placebo-controlled trial among patients with moderately severe paradoxical TB-IRIS showed that treatment with prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in a reduction in a combined endpoint of days hospitalized plus outpatient therapeutic procedures.[216] Those on prednisone experienced more rapid symptom and radiographic improvement. No reduction in mortality was demonstrated, but immediately life-threatening cases (e.g., those with neurological involvement) were excluded from this study. The above study,[216] observational data,[200] and clinical trials of patients treated with corticosteroids at the time of TB meningitis presentation where corticosteroids reduced mortality[75] suggest that corticosteroids (either intravenous dexamethasone or oral prednisone) should be used when TB-IRIS involves the CNS (e.g., enlarging tuberculoma, new or recurrent meningeal inflammation). Among all patients developing TB-IRIS, 4 weeks of prednisone treatment was insufficient in a subset, and they may require more gradual tapering of steroids over a few months **(BIII)**.[216] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms **(BIII)**. Corticosteroids should be avoided in patients with Kaposi's sarcoma, as life-threatening exacerbations can occur,[217] and also where the diagnosis of paradoxical TB-IRIS is not certain. There are case reports of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.[218-220]

Some clinicians use non-steroidal anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS **(CIII)**. Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may provide symptom relief **(CIII)**. Repeated aspirations may be required as abscesses and effusions often re-accumulate.[199]

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in patients who have unrecognized TB at the start of ART (because it is oligo-symptomatic or because the diagnosis has been missed). These patients may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[197] A common presentation is pulmonary TB with rapid symptom onset and clinical features similar to bacterial pneumonia with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.[197,216,221-223] Focal inflammatory manifestations such as abscesses and lymphadenitis may also develop.[224] The treatment should be standard TB treatment and corticosteroids, if the manifestations are life-threatening, although there is no clinical trial evidence to support steroid use **(BIII)**.

Prevention of Recurrent TB

The risk of recurrent TB among patients with HIV co-infection appears to be somewhat higher than in HIV-uninfected patients treated with the same TB treatment regimen in the same setting.[225] In TB-endemic settings, much of the increased risk of recurrent TB appears to be due to the higher risk of re-infection with a new strain of *M. tuberculosis*, with subsequent rapid progression to TB disease.[226,227] In settings with low rates of TB (such as the United States), recurrent TB due to re-infection is uncommon, even among HIV-

infected patients.[228]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV co-infection: longer TB treatment regimens, more frequent dosing of TB therapy, post-treatment isoniazid therapy, and use of ART. None of these interventions has been adequately evaluated in randomized trials in settings with low TB burdens. Post-treatment isoniazid (6–9 months of daily isoniazid therapy after the completion of standard multidrug therapy) has been shown to be effective in high-burden settings in which the risk of re-exposure is high,[229,230] suggesting that this intervention decreases the risk of re-infection. However, post-treatment isoniazid is not recommended in low-burden settings such as the United States. Given its beneficial effects on the risk of initially developing TB disease, it is very likely that ART decreases the risk of re-infection with TB disease.

Special Considerations During Pregnancy

HIV-infected pregnant women who do not have documentation of a prior negative TB screening test result or who are at high risk for repeated or ongoing exposure to individuals with active TB should be tested during pregnancy **(AIII)**. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended.[231-234] There are several studies examining the performance of the IGRAs for diagnosis of LTBI in pregnant women. In a study in HIV-infected pregnant women in Kenya, a positive IGRA result was associated with a 4.5-fold increased risk of developing active TB disease; in women with CD4 cell counts <250 cells/μL, a positive IGRA result was associated with a 5-fold increased risk of maternal mortality or active TB and a 3-fold increased risk of either active TB or mortality in infants.[235] Antenatal IGRA testing has also been demonstrated to correlate with postpartum IGRA test positivity (i.e., TB infection) in HIV-infected women.[236] In women without HIV infection, the test appears to perform well but cost issues for routine screening are an area of debate.[237] If LTBI is diagnosed during pregnancy and active TB has been ruled out, preventive treatment should be considered during pregnancy **(BIII)**. The potential risk of isoniazid toxicity must be weighed against the consequences of active TB developing during pregnancy and postpartum. Studies in HIV/TB co-infected individuals who are not receiving ART have found a high risk of progression from LTBI to active TB (10% per year) and there is a high risk of maternal and infant mortality in HIV-infected pregnant women with active TB.[238,239] However, the risk of progression from LTBI to active TB in individuals on ART is significantly decreased.[240] Given that HIV-infected pregnant women should be receiving ART for prevention of mother-to-child transmission, the risks and benefits of isoniazid therapy should be discussed. The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and frequent monitoring is needed for women receiving therapy.[241] Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[242]

The diagnostic evaluation for TB disease in pregnant women is the same as for non-pregnant adults. Chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes including preterm birth, low birthweight, and fetal growth restriction might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when treatment is not begun until late in pregnancy.[231-234,243-246] Congenital TB infection of the infant has been reported, although it appears relatively uncommon.[247] However, in one study of 107 women with active TB during pregnancy in South Africa, *M. tuberculosis* was detected in 16% of neonates (12 by culture and 4 by smear microscopy) sampled within the first 3 weeks of life.[248]

Treatment of TB disease for pregnant women should be the same as for non-pregnant women, but with attention given to the following considerations **(BIII)**:

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently in pregnancy and the postpartum period.[249] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(CIII)**.
- Rifampin is not teratogenic in humans.

- Ethambutol is teratogenic in rodents and rabbits at doses that are much higher than those used in humans. No evidence of teratogenicity has been observed in humans. Ocular toxicity has been reported in adults taking ethambutol, but changes in visual acuity have not been detected in infants born after exposure *in utero*.
- Pyrazinamide is not teratogenic in animals. Experience is limited with use in human pregnancy. Although WHO and the International Union Against Tuberculosis and Lung Diseases[250,251] have made recommendations for the routine use of pyrazinamide in pregnant women, it has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.[252] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months **(CIII)**. The decision regarding whether to include pyrazinamide for treatment should be made after consultation among obstetricians, TB specialists, and patients, taking into account gestational age and likely susceptibility pattern of the infecting strain.

Considering the information above, the preferred first-line treatment for TB in pregnancy is isoniazid, rifampin, and ethambutol.[253] Experience with using the majority of the second-line drugs for TB during pregnancy is limited.[254-257] MDR TB in pregnancy should be managed in consultation with a specialist. Therapy should not be withheld because of pregnancy **(AIII)**. The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant women:

- Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed *in utero*; its use during pregnancy should be avoided if possible **(AIII)**.
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible **(AIII)**. The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR TB **(CIII)**.
- Because arthropathy has been noted in immature animals exposed to quinolones *in utero*, quinolones are typically not recommended for pregnant women or children aged <18 years **(CIII)**. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[258,259] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[260]
- Para-aminosalicylic acid is not teratogenic in rats or rabbits.[252] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during the first trimester.[261] No specific pattern of defects and no increase in rate of defects have been detected in subjects in other human studies, indicating that this agent can be used with caution, if needed **(CIII)**.
- Ethionamide has been associated with an increased risk for several anomalies in rats after high-dose exposure but not mice and rabbits.[262-264] Case reports have documented cases of CNS defects in humans but overall experience is limited with use during human pregnancy.[265] Thus, ethionamide should be avoided unless its use is required on the basis of susceptibility testing **(CIII)**.
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

Recommendations for Treating *Mycobacterium Tuberculosis* Infection and Disease

Treating LTBI (to prevent TB disease)

Indications:

- (+) screening test[a] for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)**;
- Close contact with a person with infectious TB, regardless of screening test result **(AII)**

Preferred Therapy (Duration of Therapy = 9 Months):

- INH 300 mg PO daily + pyridoxine 25-50 mg PO daily **(AII)** *or*
- INH 900 mg PO twice weekly (by DOT) + pyridoxine 25-50 mg PO daily **(BII)**

Alternative Therapies:

- RIF 600 mg PO daily x 4 months **(BIII)** *or*
- RFB (dose adjusted based on concomitant ART) x 4 months **(BIII)** *or*
- RPT (weight-based, 900 mg max) PO weekly + INH 15 mg/kg weekly (900 mg max) + pyridoxine 50 mg weekly x 12 weeks – in patients receiving an EFV- or RAL-based ART regimen **(BIII)**
  - 32.1–49.9 kg 750 mg
  - ≥50.0 kg 900 mg
- For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities **(AII)**

Treating Active TB Disease

- After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.
- DOT is recommended for all patients requiring treatment for HIV-related TB **(AII)**.
- Please refer to the table below for TB drug dosing recommendations and to the Adult and Adolescent ARV Guidelines for dosing recommendations of ARV drugs when used with RIF or RFB.

For Drug-Sensitive TB

Intensive Phase (2 Months)

- INH + (RIF or RFB) + PZA + EMB **(AI)**; if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

Continuation Phase (For Drug-Susceptible TB)

- INH + (RIF or RFB) daily (5–7 days per week) **(AII)**

Total Duration of Therapy:

- Pulmonary, drug-susceptible TB—6 months **(BII)**
- Pulmonary TB & positive culture at 2 months of TB treatment—9 months **(BII)**
- Extrapulmonary TB w/CNS involvement—9 to 12 months **(BII)**
- Extrapulmonary TB w/bone or joint involvement—6 to 9 months **(BII)**
- Extrapulmonary TB in other sites—6 months **(BII)**

For Drug-Resistant TB

Empiric Therapy for Suspected Resistance to Rifamycin +/- Resistance to Other Drugs:

- INH + (RIF or RFB) + PZA + EMB + (moxifloxacin or levofloxacin) + (an aminoglycoside or capreomycin)
- Therapy should be modified based on drug susceptibility results
- A TB expert should be consulted

Resistant to INH

- (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months (BIII); followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months **(BII)**

Resistant to Rifamycins +/- Other Antimycobacterial Agents:

- Therapy and duration of treatment should be individualized based on drug susceptibility, clinical and microbiological responses, and with close consultation with experienced specialists **(AIII)**.

Other Considerations in TB Management

- Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS and pericardium **(AI)**.
- Dexamethasone has been used for CNS disease with the following dosing schedule: 0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks.
- Prednisone or prednisolone may be used in pericardial disease (e.g., 60 mg PO daily and taper by 10 mg per day weekly; total duration 6 weeks)
- Despite the potential of drug-drug interactions, a rifamycin remains the most potent TB drug and should remain as part of the TB regimen unless there is rifamycin-resistant isolate or the patient has a severe adverse effect that is likely to be due to the rifamycin (please refer to the table below and to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for dosing recommendations involving concomitant use of RIF or RFB and different antiretroviral drugs).
- If NVP is to be added to a patient who is receiving RIF, the lead-in dose for NVP should be omitted.
- RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving HIV PIs **(BIII)**.
- Rifamycins administered once or twice weekly can result in development of resistance in HIV-infected patients and is not recommended for patients with TB disease **(AI)**.
- Paradoxical reaction that is not severe may be treated symptomatically **(CIII)**.
- For moderately severe paradoxical reaction, use of corticosteroid may be considered.Taper over 4 weeks (or longer) based on clinical symptoms **(BIII)**.

Examples of Prednisone Dosing Strategies

- In patients on a RIF-based regimen: prednisone 1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg x 2 weeks
- In patients on a RFB + boosted PI based regimen: prednisone 1.0 mg/kg/day x 2 weeks, then 0.5 mg/kg/day x 2 weeks
- A more gradual tapering schedule over a few months may be necessary in some patients.

[a] Screening tests for LTBI include TST or IGRA; please see text for details regarding these tests.

Key to Abbreviations: ART = antiretroviral therapy; ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; EFV = efavirenz; EMB = ethambutol; INH = isoniazid; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = per os (oral); PZA = pyrazinamide; RAL = raltegravir; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; TB = tuberculosis; TIW = thrice weekly; TST = tuberculin skin test; IGRA = interferon-gamma release assays

Dosing Recommendations for Anti-Tuberculosis Drugs for Treatment of Active TB

Drug	Daily
Isoniazid	5 mg/kg (usual dose 300 mg)
Rifampin[a] **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/COBI, or TAF	10 mg/kg (usual dose 600 mg)
Rifabutin[a]	5 mg/kg (usual dose 300 mg)
without HIV PIs, EFV, RPV	
with HIV PIs	150 mg[b]
with EFV	450–600 mg
with TAF or EVG/COBI containing regimens	not recommended
Pyrazinamide (weight-based dosing)	1000 mg (18.2–25.0 mg/kg)
40–55 kg	
56–75 kg	1500 mg (20.0–26.8 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)
>90 kg	2000 mg[c]
Ethambutol	800 mg (14.5–20.0 mg/kg)
40–55 kg	
56–75 kg	1200 mg (16.0–21.4 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)
>90 kg	1600 mg[c]

[a] For more detailed guidelines on use of different antiretroviral drugs with rifamycin, clinicians should refer to the Drug Interactions section of the Adult and Adolescent ARV Guidelines

[b] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

[c] Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide

References

1. World Health Organization. Global Tuberculosis Report. Geneva: World Health Organization;2015. Available at http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf.
2. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. Mar 2 1989;320(9):545-550. Available at http://www.ncbi.nlm.nih.gov/pubmed/2915665.
3. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis*. Jan 15 2005;191(2):150-158. Available at http://www.ncbi.nlm.nih.gov/pubmed/15609223.
4. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. Jan 1 2000;23(1):75-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/10708059.
5. Jones JL, Hanson DL, Dworkin MS, DeCock KM, Adult/Adolescent Spectrum of HIVDG. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis*. Nov 2000;4(11):1026-1031. Available at http://www.ncbi.nlm.nih.gov/pubmed/11092714.
6. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. Jul 15 2010;363(3):257-265. Available at http://www.ncbi.nlm.nih.gov/pubmed/20647201.
7. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet*. Jun 15 2002;359(9323):2059-2064. Available at http://www.ncbi.nlm.nih.gov/pubmed/12086758.
8. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. *Am J Respir Crit Care Med*. Jul 1 2005;172(1):123-127. Available at http://www.ncbi.nlm.nih.gov/pubmed/15805184.
9. Scott C, Kirking HL, Jeffries C, et al. Tuberculosis trends--United States, 2014. *MMWR Morb Mortal Wkly Rep*. Mar 20 2015;64(10):265-269. Available at http://www.ncbi.nlm.nih.gov/pubmed/25789741.
10. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One*. 2015;10(11):e0140881. Available at http://www.ncbi.nlm.nih.gov/pubmed/26536035.
11. Albalak R, O'Brien RJ, Kammerer JS, et al. Trends in tuberculosis/human immunodeficiency virus comorbidity, United States, 1993-2004. *Arch Intern Med*. Dec 10 2007;167(22):2443-2452. Available at http://www.ncbi.nlm.nih.gov/pubmed/18071166.
12. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2013. Atlanta, GA: U.S. Department of Health and Human Services, CDC;2014. Available at http://www.cdc.gov/tb/statistics/reports/2013/pdf/report2013.pdf.
13. Trieu L, Li J, Hanna DB, Harris TG. Tuberculosis rates among HIV-infected persons in New York City, 2001-2005. *Am J Public Health*. Jun 2010;100(6):1031-1034. Available at http://www.ncbi.nlm.nih.gov/pubmed/20395574.
14. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep*. Jun 9 2000;49(RR-6):1-51. Available at http://www.ncbi.nlm.nih.gov/pubmed/10881762.

15. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. May 13 2004;350(20):2060-2067. Available at http://www.ncbi.nlm.nih.gov/pubmed/15141044.

16. Day JH, Grant AD, Fielding KL, et al. Does tuberculosis increase HIV load? *J Infect Dis*. Nov 1 2004;190(9):1677-1684. Available at http://www.ncbi.nlm.nih.gov/pubmed/15478075.

17. Lopez-Gatell H, Cole SR, Margolick JB, et al. Effect of tuberculosis on the survival of HIV-infected men in a country with low tuberculosis incidence. *AIDS*. Sep 12 2008;22(14):1869-1873. Available at http://www.ncbi.nlm.nih.gov/pubmed/18753866.

18. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at http://www.ncbi.nlm.nih.gov/pubmed/20091503.

19. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. Jul 11 2007;21(11):1441-1448. Available at http://www.ncbi.nlm.nih.gov/pubmed/17589190.

20. Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis*. Oct 2013;13(10):852-858. Available at http://www.ncbi.nlm.nih.gov/pubmed/23954450.

21. Temprano Anrs Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.

22. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. Aug 23 2014;384(9944):682-690. Available at http://www.ncbi.nlm.nih.gov/pubmed/24835842.

23. Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis*. Feb 15 2015;60(4):639-645. Available at http://www.ncbi.nlm.nih.gov/pubmed/25365974.

24. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. Jul 31 1997;337(5):315-320. Available at http://www.ncbi.nlm.nih.gov/pubmed/9233868.

25. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. May 7 2011;377(9777):1588-1598. Available at http://www.ncbi.nlm.nih.gov/pubmed/21492926.

26. Fisk TL, Hon HM, Lennox JL, Fordham von Reyn C, Horsburgh CR, Jr. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. May 2 2003;17(7):1102-1104. Available at http://www.ncbi.nlm.nih.gov/pubmed/12700468.

27. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS*. Sep 27 2002;16(14):1976-1979. Available at http://www.ncbi.nlm.nih.gov/pubmed/12351964.

28. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. Aug 1 1993;119(3):185-193. Available at http://www.ncbi.nlm.nih.gov/pubmed/8100692.

29. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. *Lancet*. Apr 5 2003;361(9364):1168-1173. Available at http://www.ncbi.nlm.nih.gov/pubmed/12686038.

30. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thorac Soc*. 2006;3(1):103-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/16493157.

31. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med*. Mar 6 2007;146(5):340-354. Available at http://www.ncbi.nlm.nih.gov/pubmed/17339619.

32. Raby E, Moyo M, Devendra A, et al. The effects of HIV on the sensitivity of a whole blood IFN-gamma release assay in Zambian adults with active tuberculosis. *PLoS One*. 2008;3(6):e2489. Available at http://www.ncbi.nlm.nih.gov/

pubmed/18560573.

33. Dorman SE, Belknap R, Graviss EA, et al. Interferon-gamma release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med*. Jan 1 2014;189(1):77-87. Available at http://www.ncbi.nlm.nih.gov/pubmed/24299555.
34. Gray J, Reves R, Johnson S, Belknap R. Identification of false-positive QuantiFERON-TB Gold In-Tube assays by repeat testing in HIV-infected patients at low risk for tuberculosis. *Clin Infect Dis*. Feb 1 2012;54(3):e20-23. Available at http://www.ncbi.nlm.nih.gov/pubmed/22057704.
35. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. Apr 1 2007;175(7):737-742. Available at http://www.ncbi.nlm.nih.gov/pubmed/17218620.
36. Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis*. 2009;9:15. Available at http://www.ncbi.nlm.nih.gov/pubmed/19208218.
37. Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. *PLoS One*. 2008;3(1):e1379. Available at http://www.ncbi.nlm.nih.gov/pubmed/18167540.
38. Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis*. Apr 1 2009;48(7):954-962. Available at http://www.ncbi.nlm.nih.gov/pubmed/19245343.
39. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis. *Am J Respir Crit Care Med*. May 15 2008;177(10):1164-1170. Available at http://www.ncbi.nlm.nih.gov/pubmed/18276940.
40. Leung CC, Yam WC, Yew WW, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med*. Sep 15 2010;182(6):834-840. Available at http://www.ncbi.nlm.nih.gov/pubmed/20508217.
41. Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. Nov 15 2005;143(10):729-736. Available at http://www.ncbi.nlm.nih.gov/pubmed/16287794.
42. Backus LI, Boothroyd DB, Phillips BR, et al. National quality forum performance measures for HIV/AIDS care: the Department of Veterans Affairs' experience. *Arch Intern Med*. Jul 26 2010;170(14):1239-1246. Available at http://www.ncbi.nlm.nih.gov/pubmed/20660844.
43. Lee LM, Lobato MN, Buskin SE, Morse A, Costa OS. Low adherence to guidelines for preventing TB among persons with newly diagnosed HIV infection, United States. *Int J Tuberc Lung Dis*. Feb 2006;10(2):209-214. Available at http://www.ncbi.nlm.nih.gov/pubmed/16499263.
44. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm Rep*. Jun 25 2010;59(RR-5):1-25. Available at http://www.ncbi.nlm.nih.gov/pubmed/20577159.
45. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011;8(1):e1000391. Available at http://www.ncbi.nlm.nih.gov/pubmed/21267059.
46. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. Sep 18 1997;337(12):801-808. Available at http://www.ncbi.nlm.nih.gov/pubmed/9295239.
47. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS*. Dec 24 1998;12(18):2447-2457. Available at http://www.ncbi.nlm.nih.gov/pubmed/9875583.
48. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. *Int J Tuberc Lung Dis*. Oct 2007;11(10):1114-1120. Available at http://www.ncbi.nlm.nih.gov/pubmed/17945069.
49. Horsburgh CR, Jr., Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. Feb 2010;137(2):401-409. Available at http://www.ncbi.nlm.nih.gov/pubmed/19793865.

50. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA*. Mar 15 2000;283(11):1445-1450. Available at http://www.ncbi.nlm.nih.gov/pubmed/10732934.

51. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. Nov 18 2008;149(10):689-697. Available at http://www.ncbi.nlm.nih.gov/pubmed/19017587.

52. Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *Int J Infect Dis*. Apr 2010;14(4):e292-297. Available at http://www.ncbi.nlm.nih.gov/pubmed/19656705.

53. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of M. tuberculosis infection in HIV co-infected persons. *AIDS*. Mar 17 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26990624.

54. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. Jul 7 2011;365(1):11-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/21732833.

55. Sterling T, Benson C, Scott N, et al. Three Months of Weekly Rifapentine + INH for M. tuberculosis Infection in HIV-Infected Persons. 21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014, 2014; Boston, Massachusetts.

56. Podany AT, Bao Y, Swindells S, et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. *Clin Infect Dis*. Oct 15 2015;61(8):1322-1327. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082504.

57. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine Once-Weekly Dosing Effect on Efavirenz Emtricitabine and Tenofovir PKs. 21st Conference on Retroviruses and Opportunistic Infections; 2014; Boston, MA.

58. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. Apr 2014;69(4):1079-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/24343893.

59. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. Mar 13 2009;23(5):631-636. Available at http://www.ncbi.nlm.nih.gov/pubmed/19525621.

60. Samandari T, Mosimaneotsile B, al. e. Randomized placebo-controlled trial of 8 vs. 36 months of isoniazid TB preventative therapy for HIV-infected adults in Botswana. 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Fransisco, CA.

61. Bliven-Sizemore EE, Sterling TR, Shang N, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int J Tuberc Lung Dis*. Sep 2015;19(9):1039-1044, i-v. Available at http://www.ncbi.nlm.nih.gov/pubmed/26260821.

62. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. Oct 15 2006;174(8):935-952. Available at http://www.ncbi.nlm.nih.gov/pubmed/17021358.

63. Rangaka MX, Wilkinson RJ, Glynn JR, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. *Clin Infect Dis*. Dec 2012;55(12):1698-1706. Available at http://www.ncbi.nlm.nih.gov/pubmed/22955441.

64. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. Feb 25 2010;362(8):707-716. Available at http://www.ncbi.nlm.nih.gov/pubmed/20181972.

65. Corbett EL, Charalambous S, Moloi VM, et al. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med*. Sep 15 2004;170(6):673-679. Available at http://www.ncbi.nlm.nih.gov/pubmed/15191919.

66. Ahuja SS, Ahuja SK, Phelps KR, Thelmo W, Hill AR. Hemodynamic confirmation of septic shock in disseminated tuberculosis. *Crit Care Med*. Jun 1992;20(6):901-903. Available at http://www.ncbi.nlm.nih.gov/pubmed/1597048.

67. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, Van de Perre P. Pulmonary tuberculosis in Kigali, Rwanda. Impact of human immunodeficiency virus infection on clinical and radiographic presentation. *Am Rev Respir Dis*. Jul 1992;146(1):53-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/1626814.

68. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. Nov 1993;148(5):1292-1297. Available at http://www.ncbi.nlm.nih.gov/pubmed/7902049.

69. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. Aug 1997;25(2):242-246. Available at http://www.ncbi.nlm.nih.gov/pubmed/9332519.

70. Post F, Wood R, Pillay G. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis*. 1995;76:518-21.

71. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. *Int J Tuberc Lung Dis*. Apr 2008;12(4):397-403. Available at http://www.ncbi.nlm.nih.gov/pubmed/18371265.

72. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine (Baltimore)*. Nov 1991;70(6):384-397. Available at http://www.ncbi.nlm.nih.gov/pubmed/1956280.

73. Whalen C, Horsburgh CR, Jr., Hom D, Lahart C, Simberkoff M, Ellner J. Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. *AIDS*. Mar 15 1997;11(4):455-460. Available at http://www.ncbi.nlm.nih.gov/pubmed/9084792.

74. Kourbatova EV, Leonard MK, Jr., Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. *Eur J Epidemiol*. 2006;21(9):715-721. Available at http://www.ncbi.nlm.nih.gov/pubmed/17072539.

75. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. Oct 21 2004;351(17):1741-1751. Available at http://www.ncbi.nlm.nih.gov/pubmed/15496623.

76. Lewis JJ, Charalambous S, Day JH, et al. HIV infection does not affect active case finding of tuberculosis in South African gold miners. *Am J Respir Crit Care Med*. Dec 15 2009;180(12):1271-1278. Available at http://www.ncbi.nlm.nih.gov/pubmed/19745207.

77. Cavanaugh JS, Modi S, Musau S, et al. Comparative Yield of Different Diagnostic Tests for Tuberculosis among People Living with HIV in Western Kenya. *PLoS One*. 2016;11(3):e0152364. Available at http://www.ncbi.nlm.nih.gov/pubmed/27023213.

78. Henostroza G, Harris JB, Chitambi R, et al. High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach. *Int J Tuberc Lung Dis*. Aug 2016;20(8):1033-1039. Available at http://www.ncbi.nlm.nih.gov/pubmed/27393536.

79. Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. *J Trop Med Hyg*. Feb 1993;96(1):1-11. Available at http://www.ncbi.nlm.nih.gov/pubmed/8429569.

80. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis*. Mar 2009;9(3):173-184. Available at http://www.ncbi.nlm.nih.gov/pubmed/19246021.

81. Monkongdee P, McCarthy KD, Cain KP, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. *Am J Respir Crit Care Med*. Nov 1 2009;180(9):903-908. Available at http://www.ncbi.nlm.nih.gov/pubmed/19628775.

82. Leeds IL, Magee MJ, Kurbatova EV, et al. Site of extrapulmonary tuberculosis is associated with HIV infection. *Clin Infect Dis*. Jul 2012;55(1):75-81. Available at http://www.ncbi.nlm.nih.gov/pubmed/22423123.

83. Naing C, Mak JW, Maung M, Wong SF, Kassim AI. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung*. Feb 2013;191(1):27-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/23180033.

84. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis*. Oct 1992;15(4):601-605. Available at http://www.ncbi.nlm.nih.gov/pubmed/1420673.

85. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. Sep 9 2010;363(11):1005-1015. Available at http://www.ncbi.nlm.nih.gov/pubmed/20825313.

86. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess*. Jan 2007;11(3):1-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266837.

87. Centers for Disease C, Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep*. Jan 16 2009;58(1):7-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/19145221.

88. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. *Policy statement*. 2011. http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf. Accessed 2/18/2016.

89. Food and Drug Adminstration. FDA permits marketing of first U.S. test labeled for simultaneous detection of tuberculosis bacteria and resistance to the antibiotic rifampin. 2013. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm362602.htm.

90. Food and Drug Adminstration. New data shows test can help physicians remove patients with suspected TB from isolation earlier. 2015. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434226.htm.

91. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;1:CD009593. Available at http://www.ncbi.nlm.nih.gov/pubmed/24448973.

92. Luetkemeyer AF, Kendall MA, Wu X, et al. Evaluation of two line probe assays for rapid detection of Mycobacterium tuberculosis, tuberculosis (TB) drug resistance, and non-TB Mycobacteria in HIV-infected individuals with suspected TB. *J Clin Microbiol*. Apr 2014;52(4):1052-1059. Available at http://www.ncbi.nlm.nih.gov/pubmed/24430455.

93. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. *BMC Med*. 2013;11:231. Available at http://www.ncbi.nlm.nih.gov/pubmed/24168211.

94. Maynard-Smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709. Available at http://www.ncbi.nlm.nih.gov/pubmed/25599808.

95. Drain PK, Losina E, Coleman SM, et al. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. *BMC Infect Dis*. 2014;14:110. Available at http://www.ncbi.nlm.nih.gov/pubmed/24571362.

96. Drain PK, Losina E, Coleman SM, et al. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis. *J Acquir Immune Defic Syndr*. Mar 1 2015;68(3):274-280. Available at http://www.ncbi.nlm.nih.gov/pubmed/25415288.

97. Lawn SD, Dheda K, Kerkhoff AD, et al. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infect Dis*. 2013;13:407. Available at http://www.ncbi.nlm.nih.gov/pubmed/24004840.

98. Kerkhoff AD, Wood R, Vogt M, Lawn SD. Prognostic value of a quantitative analysis of lipoarabinomannan in urine from patients with HIV-associated tuberculosis. *PLoS One*. 2014;9(7):e103285. Available at http://www.ncbi.nlm.nih.gov/pubmed/25075867.

99. Peter JG, Theron G, van Zyl-Smit R, et al. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. *Eur Respir J*. Nov 2012;40(5):1211-1220. Available at http://www.ncbi.nlm.nih.gov/pubmed/22362849.

100. Shah M, Ssengooba W, Armstrong D, et al. Comparative performance of urinary lipoarabinomannan assays and Xpert MTB/RIF in HIV-infected individuals. *AIDS*. Jun 1 2014;28(9):1307-1314. Available at http://www.ncbi.nlm.nih.gov/pubmed/24637544.

101. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. Jul 15 2008;149(2):123-134. Available at http://www.ncbi.nlm.nih.gov/pubmed/18626051.

102. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. Jan 1 2010;181(1):80-86. Available at http://www.ncbi.nlm.nih.gov/pubmed/19833824.

103. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N*

Engl J Med. Oct 12 2006;355(15):1539-1550. Available at http://www.ncbi.nlm.nih.gov/pubmed/17035648.

104. Mathema B, Kurepina NE, Bifani PJ, Kreiswirth BN. Molecular epidemiology of tuberculosis: current insights. *Clin Microbiol Rev*. Oct 2006;19(4):658-685. Available at http://www.ncbi.nlm.nih.gov/pubmed/17041139.
105. Barnard M, Warren R, Gey Van Pittius N, et al. Genotype MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory. *Am J Respir Crit Care Med*. Dec 15 2012;186(12):1298-1305. Available at http://www.ncbi.nlm.nih.gov/pubmed/23087027.
106. World Health Organization. *The Use of Molecular Line Probe Assay for the Detection of Resistance to Second-Line Anti-Tuberculosis Drugs*. Geneva 2013. Available at http://apps.who.int/iris/bitstream/10665/78099/1/WHO_HTM_TB_2013.01.eng.pdf.
107. Osman M, Simpson JA, Caldwell J, Bosman M, Nicol MP. GeneXpert MTB/RIF version G4 for identification of rifampin-resistant tuberculosis in a programmatic setting. *J Clin Microbiol*. Feb 2014;52(2):635-637. Available at http://www.ncbi.nlm.nih.gov/pubmed/24478501.
108. Van Deun A, Aung KJ, Bola V, et al. Rifampin drug resistance tests for tuberculosis: challenging the gold standard. *J Clin Microbiol*. Aug 2013;51(8):2633-2640. Available at http://www.ncbi.nlm.nih.gov/pubmed/23761144.
109. Rigouts L, Gumusboga M, de Rijk WB, et al. Rifampin resistance missed in automated liquid culture system for Mycobacterium tuberculosis isolates with specific rpoB mutations. *J Clin Microbiol*. Aug 2013;51(8):2641-2645. Available at http://www.ncbi.nlm.nih.gov/pubmed/23761146.
110. Williamson DA, Roberts SA, Bower JE, et al. Clinical failures associated with rpoB mutations in phenotypically occult multidrug-resistant Mycobacterium tuberculosis. *Int J Tuberc Lung Dis*. Feb 2012;16(2):216-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/22137551.
111. Ho J, Jelfs P, Sintchencko V. Phenotypically occult multidrug-resistant Mycobacterium tuberculosis: dilemmas in diagnosis and treatment. *J Antimicrob Chemother*. Dec 2013;68(12):2915-2920. Available at http://www.ncbi.nlm.nih.gov/pubmed/23838950.
112. Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med*. Apr 1 2010;181(7):743-751. Available at http://www.ncbi.nlm.nih.gov/pubmed/19965813.
113. Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis*. Mar 1 2004;38(5):731-736. Available at http://www.ncbi.nlm.nih.gov/pubmed/14986259.
114. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. *Clin Infect Dis*. Jul 1 2005;41(1):83-91. Available at http://www.ncbi.nlm.nih.gov/pubmed/15937767.
115. Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. May 1 2010;50(9):1288-1299. Available at http://www.ncbi.nlm.nih.gov/pubmed/20353364.
116. Vashishtha R, Mohan K, Singh B, et al. Efficacy and safety of thrice weekly DOTS in tuberculosis patients with and without HIV co-infection: an observational study. *BMC Infect Dis*. 2013;13:468. Available at http://www.ncbi.nlm.nih.gov/pubmed/24099345.
117. Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. Dec 15 2014;59(12):1798-1804. Available at http://www.ncbi.nlm.nih.gov/pubmed/25156114.
118. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. May 29 1999;353(9167):1843-1847. Available at http://www.ncbi.nlm.nih.gov/pubmed/10359410.
119. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med*. Feb 1 2006;173(3):350-356. Available at http://www.ncbi.nlm.nih.gov/pubmed/16109981.
120. Reynolds HE, Chrdle A, Egan D, et al. Effect of intermittent rifampicin on the pharmacokinetics and safety of raltegravir. *J Antimicrob Chemother*. Feb 2015;70(2):550-554. Available at http://www.ncbi.nlm.nih.gov/pubmed/25261424.

121. el-Sadr WM, Perlman DC, Matts JP, et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. May 1998;26(5):1148-1158. Available at http://www.ncbi.nlm.nih.gov/pubmed/9597244.

122. Perriens JH, St Louis ME, Mukadi YB, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *N Engl J Med*. Mar 23 1995;332(12):779-784. Available at http://www.ncbi.nlm.nih.gov/pubmed/7862181.

123. Jawahar MS, Banurekha VV, Paramasivan CN, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. *PLoS One*. 2013;8(7):e67030. Available at http://www.ncbi.nlm.nih.gov/pubmed/23843980.

124. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. Oct 23 2014;371(17):1588-1598. Available at http://www.ncbi.nlm.nih.gov/pubmed/25337748.

125. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. Oct 23 2014;371(17):1577-1587. Available at http://www.ncbi.nlm.nih.gov/pubmed/25196020.

126. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. Oct 23 2014;371(17):1599-1608. Available at http://www.ncbi.nlm.nih.gov/pubmed/25337749.

127. Heemskerk AD, Bang ND, Mai NT, et al. Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. *N Engl J Med*. Jan 14 2016;374(2):124-134. Available at http://www.ncbi.nlm.nih.gov/pubmed/26760084.

128. Ruslami R, Ganiem AR, Aarnoutse RE, van Crevel R, study t. Rifampicin and moxifloxacin for tuberculous meningitis--authors' reply. *Lancet Infect Dis*. Jul 2013;13(7):570. Available at http://www.ncbi.nlm.nih.gov/pubmed/23809224.

129. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. *N Engl J Med*. Sep 18 2014;371(12):1121-1130. Available at http://www.ncbi.nlm.nih.gov/pubmed/25178809.

130. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706. Available at http://www.ncbi.nlm.nih.gov/pubmed/20181971.

131. Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis*. Jul 2014;14(7):563-571. Available at http://www.ncbi.nlm.nih.gov/pubmed/24810491.

132. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. Aug 27 2015;373(9):795-807. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.

133. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. Apr 2014;14(4):281-290. Available at http://www.ncbi.nlm.nih.gov/pubmed/24602844.

134. Havlir DV, Ive P, al. e. International randomized trial of immediate vs. early antiretroviral therapy in HIV+ patients treated for tuberculosis: ACTG 5221 "STRIDE" study. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections 2011; Boston, MA.

135. Blanc FX, Sok T, et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of higly active antiretrotherapy (HAART) in severely immunosuppresed HIV-infected adults with newly diagnosed tuberculosis. 18th International AIDS Conference; 2010; Vienna, Austria.

136. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med*. Jun 1 2007;175(11):1199-1206. Available at http://www.ncbi.nlm.nih.gov/pubmed/17290042.

137. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1471-1481. Available at http://www.ncbi.nlm.nih.gov/pubmed/22010913.

138. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1482-1491. Available at http://www.ncbi.nlm.nih.gov/pubmed/22010914.

139. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. Jun 2011;52(11):1374-1383. Available at http://www.ncbi.

nlm.nih.gov/pubmed/21596680.

140. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. Aug 6 2008;300(5):530-539. Available at http://www.ncbi.nlm.nih.gov/pubmed/18677025.
141. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41(9):681-690. Available at http://www.ncbi.nlm.nih.gov/pubmed/12126459.
142. Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14(5):687-695. Available at http://www.ncbi.nlm.nih.gov/pubmed/19704172.
143. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. *Antimicrob Agents Chemother*. Mar 2009;53(3):863-868. Available at http://www.ncbi.nlm.nih.gov/pubmed/19124658.
144. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. Aug 2013;57(4):586-593. Available at http://www.ncbi.nlm.nih.gov/pubmed/23592830.
145. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. Jan 2 2006;20(1):131-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/16327334.
146. Manosuthi W, Sungkanuparph S, Thakkinstian A, et al. Plasma nevirapine levels and 24-week efficacy in HIV-infected patients receiving nevirapine-based highly active antiretroviral therapy with or without rifampicin. *Clin Infect Dis*. Jul 15 2006;43(2):253-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/16779754.
147. Shipton LK, Wester CW, Stock S, et al. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis*. Mar 2009;13(3):360-366. Available at http://www.ncbi.nlm.nih.gov/pubmed/19275797.
148. Bonnet M, Bhatt N, Baudin E, et al. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a randomised non-inferiority trial. *Lancet Infect Dis*. Apr 2013;13(4):303-312. Available at http://www.ncbi.nlm.nih.gov/pubmed/23433590.
149. Swaminathan S, Padmapriyadarsini C, Venkatesan P, et al. Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial. *Clin Infect Dis*. Oct 2011;53(7):716-724. Available at http://www.ncbi.nlm.nih.gov/pubmed/21890776.
150. Bhatt NB, Baudin E, Meggi B, et al. Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship. *J Antimicrob Chemother*. Jan 2015;70(1):225-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/25239466.
151. Jiang HY, Zhang MN, Chen HJ, Yang Y, Deng M, Ruan B. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. *Int J Infect Dis*. Aug 2014;25:130-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/24911886.
152. Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis*. Jun 2014;14(6):459-467. Available at http://www.ncbi.nlm.nih.gov/pubmed/24726095.
153. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2007(4):CD005159. Available at http://www.ncbi.nlm.nih.gov/pubmed/17943842.
154. Singh R, Marshall N, Smith CJ, et al. No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfected patients. *AIDS*. Jan 28 2013;27(3):481-484. Available at http://www.ncbi.nlm.nih.gov/pubmed/23014518.
155. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother*. May 2004;48(5):1553-1560. Available at http://www.ncbi.nlm.nih.gov/pubmed/15105105.
156. Decloedt EH, McIlleron H, Smith P, Merry C, Orrell C, Maartens G. Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampin with adjusted doses of lopinavir-ritonavir tablets. *Antimicrob Agents Chemother*. Jul

2011;55(7):3195-3200. Available at http://www.ncbi.nlm.nih.gov/pubmed/21537021.

157. Nijland HM, L'Homme R F, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS*. May 11 2008;22(8):931-935. Available at http://www.ncbi.nlm.nih.gov/pubmed/18453852.
158. Haas DW, Koletar SL, Laughlin L, et al. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr*. Mar 1 2009;50(3):290-293. Available at http://www.ncbi.nlm.nih.gov/pubmed/19194314.
159. Schmitt C, Riek M, Winters K, Schutz M, Grange S. Unexpected Hepatotoxicity of Rifampin and Saquinavir/Ritonavir in Healthy Male Volunteers. *Arch Drug Inf*. Mar 2009;2(1):8-16. Available at http://www.ncbi.nlm.nih.gov/pubmed/19381336.
160. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlleron H. The safety, effectiveness and concentrations of adjusted lopinavir/ritonavir in HIV-infected adults on rifampicin-based antitubercular therapy. *PLoS One*. 2012;7(3):e32173. Available at http://www.ncbi.nlm.nih.gov/pubmed/22412856.
161. Sunpath H, Winternheimer P, Cohen S, et al. Double-dose lopinavir-ritonavir in combination with rifampicin-based anti-tuberculosis treatment in South Africa. *Int J Tuberc Lung Dis*. Jun 2014;18(6):689-693. Available at http://www.ncbi.nlm.nih.gov/pubmed/24903940.
162. Abbott. Lopinavir/ritonavir package insert. 2011.
163. Bristol-Myers Squibb. Atazanavir package insert. 2011.
164. Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob Agents Chemother*. Oct 2010;54(10):4440-4445. Available at http://www.ncbi.nlm.nih.gov/pubmed/20660678.
165. Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob Agents Chemother*. Feb 2008;52(2):534-538. Available at http://www.ncbi.nlm.nih.gov/pubmed/18056271.
166. Lin HC, Lu PL, Chang CH. Uveitis associated with concurrent administration of rifabutin and lopinavir/ritonavir (Kaletra). Eye (Lond). Dec 2007;21(12):1540-1541. Available at http://www.ncbi.nlm.nih.gov/pubmed/17962822.
167. Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS One*. 2014;9(1):e84866. Available at http://www.ncbi.nlm.nih.gov/pubmed/24465443.
168. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at http://www.ncbi.nlm.nih.gov/pubmed/25406657.
169. Jenny-Avital ER, Joseph K. Rifamycin-resistant Mycobacterium tuberculosis in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis*. May 15 2009;48(10):1471-1474. Available at http://www.ncbi.nlm.nih.gov/pubmed/19368504.
170. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis*. Nov 1 2009;49(9):1305-1311. Available at http://www.ncbi.nlm.nih.gov/pubmed/19807276.
171. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother*. Jul 2009;53(7):2852-2856. Available at http://www.ncbi.nlm.nih.gov/pubmed/19433563.
172. Brainard DM, Wenning LA, Stone JA, Wagner JA, Iwamoto M. Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol*. Oct 2011;51(10):1376-1402. Available at http://www.ncbi.nlm.nih.gov/pubmed/21209233.
173. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. Jan 1 2013;62(1):21-27. Available at http://www.ncbi.nlm.nih.gov/pubmed/23075918.

174. Johnson JL, Okwera A, Nsubuga P, et al. Efficacy of an unsupervised 8-month rifampicin-containing regimen for the treatment of pulmonary tuberculosis in HIV-infected adults. Uganda-Case Western Reserve University Research Collaboration. *Int J Tuberc Lung Dis*. Nov 2000;4(11):1032-1040. Available at http://www.ncbi.nlm.nih.gov/pubmed/11092715.

175. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*. Oct 2-8 2004;364(9441):1244-1251. Available at http://www.ncbi.nlm.nih.gov/pubmed/15464185.

176. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. Aug 17 2002;360(9332):528-534. Available at http://www.ncbi.nlm.nih.gov/pubmed/12241657.

177. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis*. Aug 15 2007;196 Suppl 1:S63-75. Available at http://www.ncbi.nlm.nih.gov/pubmed/17624828.

178. Bliven-Sizemore EE, Johnson JL, Goldberg S, et al. Effect of HIV infection on tolerability and bacteriologic outcomes of tuberculosis treatment. *Int J Tuberc Lung Dis*. Apr 2012;16(4):473-479. Available at http://www.ncbi.nlm.nih.gov/pubmed/22325844.

179. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. Feb 1991;99(2):465-471. Available at http://www.ncbi.nlm.nih.gov/pubmed/1824929.

180. Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis*. Mar 15 2010;50(6):833-839. Available at http://www.ncbi.nlm.nih.gov/pubmed/20156055.

181. Tahaoglu K, Atac G, Sevim T, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. Jan 2001;5(1):65-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/11263519.

182. Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis*. Dec 2011;15(12):1649-1657. Available at http://www.ncbi.nlm.nih.gov/pubmed/22118173.

183. Menzies D, Benedetti A, Paydar A, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS Med*. Sep 2009;6(9):e1000150. Available at http://www.ncbi.nlm.nih.gov/pubmed/20101802.

184. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva 2011. Available at http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf?ua=1.

185. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012;9(8):e1001300. Available at http://www.ncbi.nlm.nih.gov/pubmed/22952439.

186. Kempker RR, Vashakidze S, Solomonia N, Dzidzikashvili N, Blumberg HM. Surgical treatment of drug-resistant tuberculosis. *Lancet Infect Dis*. Feb 2012;12(2):157-166. Available at http://www.ncbi.nlm.nih.gov/pubmed/22281142.

187. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis – 2016 Update. 2016. Available at http://www.who.int/tb/areas-of-work/drug-resistant-tb/MDRTBguidelines2016.pdf.

188. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis*. Oct 2014;18(10):1180-1187. Available at http://www.ncbi.nlm.nih.gov/pubmed/25216831.

189. Sirturo [package insert]; Janssen Therapeutics; Titusville, NJ; 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf.

190. Centers for Disease Control and Prevention. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. *MMWR Recomm Rep*. Oct 25 2013;62(RR-09):1-12. Available at http://www.ncbi.nlm.nih.gov/pubmed/24157696.

191. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. Nov 2014;58(11):6406-6412. Available at http://www.ncbi.nlm.nih.gov/pubmed/25114140.

192. Pandie M, Wiesner L, McIlleron H, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J Antimicrob Chemother*. Apr 2016;71(4):1037-1040. Available at http://www.ncbi.nlm.nih.gov/pubmed/26747099.

193. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med*. Jun 7 2012;366(23):2151-2160. Available at http://www.ncbi.nlm.nih.gov/pubmed/22670901.

194. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. Aug 20 2004;18(12):1615-1627. Available at http://www.ncbi.nlm.nih.gov/pubmed/15280772.

195. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. Jun 2005;5(6):361-373. Available at http://www.ncbi.nlm.nih.gov/pubmed/15919622.

196. Meintjes G, Rabie H, Wilkinson RJ, Cotton MF. Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy. *Clin Chest Med*. Dec 2009;30(4):797-810, x. Available at http://www.ncbi.nlm.nih.gov/pubmed/19925968.

197. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. Aug 2008;8(8):516-523. Available at http://www.ncbi.nlm.nih.gov/pubmed/18652998.

198. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. Apr 2010;10(4):251-261. Available at http://www.ncbi.nlm.nih.gov/pubmed/20334848.

199. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. Dec 2007;11(12):1282-1289. Available at http://www.ncbi.nlm.nih.gov/pubmed/18229435.

200. Pepper DJ, Marais S, Maartens G, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. Jun 1 2009;48(11):e96-107. Available at http://www.ncbi.nlm.nih.gov/pubmed/19405867.

201. Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. *AIDS*. Nov 12 2007;21(17):2362-2363. Available at http://www.ncbi.nlm.nih.gov/pubmed/18090294.

202. Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*. Mar 1 2009;48(5):667-676. Available at http://www.ncbi.nlm.nih.gov/pubmed/19191655.

203. Sonderup MW, Wainwright H, Hall P, Hairwadzi H, Spearman CW. A clinicopathological cohort study of liver pathology in 301 patients with human immunodeficiency virus/acquired immune deficiency syndrome. *Hepatology*. May 2015;61(5):1721-1729. Available at http://www.ncbi.nlm.nih.gov/pubmed/25644940.

204. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol*. 2015;10(6):1077-1099. Available at http://www.ncbi.nlm.nih.gov/pubmed/26059627.

205. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. Jul 1998;158(1):157-161. Available at http://www.ncbi.nlm.nih.gov/pubmed/9655723.

206. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. Aug 2004;59(8):704-707. Available at http://www.ncbi.nlm.nih.gov/pubmed/15282393.

207. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. Dec 1 2004;39(11):1709-1712. Available at http://www.ncbi.nlm.nih.gov/pubmed/15578375.

208. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. Jan 30 2007;21(3):335-341. Available at http://www.ncbi.nlm.nih.gov/pubmed/17255740.

209. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect*. Dec 2006;53(6):357-363. Available at http://www.ncbi.nlm.nih.gov/pubmed/16487593.

210. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. *Braz J Infect Dis*. Oct 2007;11(5):462-465. Available at http://www.ncbi.nlm.nih.gov/pubmed/17962870.

211. Olalla J, Pulido F, Rubio R, et al. Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. *Int J Tuberc Lung Dis*. Jan 2002;6(1):71-75. Available at http://www.ncbi.nlm.nih.gov/pubmed/11931404.

212. Huyst V, Lynen L, Bottieau E, Zolfo M, Kestens L, Colebunders R. Immune reconstitution inflammatory syndrome in an HIV/TB co-infected patient four years after starting antiretroviral therapy. *Acta Clin Belg*. Mar-Apr 2007;62(2):126-129. Available at http://www.ncbi.nlm.nih.gov/pubmed/17547295.

213. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at http://www.ncbi.nlm.nih.gov/pubmed/15918332.

214. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. *J Acquir Immune Defic Syndr*. Apr 1 2014;65(4):423-428. Available at http://www.ncbi.nlm.nih.gov/pubmed/24226057.

215. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One*. 2013;8(5):e63541. Available at http://www.ncbi.nlm.nih.gov/pubmed/23691062.

216. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Sep 24 2010;24(15):2381-2390. Available at http://www.ncbi.nlm.nih.gov/pubmed/20808204.

217. Volkow PF, Cornejo P, Zinser JW, Ormsby CE, Reyes-Teran G. Life-threatening exacerbation of Kaposi's sarcoma after prednisone treatment for immune reconstitution inflammatory syndrome. *AIDS*. Mar 12 2008;22(5):663-665. Available at http://www.ncbi.nlm.nih.gov/pubmed/18317012.

218. Brunel AS, Reynes J, Tuaillon E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*. Oct 23 2012;26(16):2110-2112. Available at http://www.ncbi.nlm.nih.gov/pubmed/22874513.

219. Hsu DC, Faldetta KF, Pei L, et al. A Paradoxical Treatment for a Paradoxical Condition: Infliximab Use in Three Cases of Mycobacterial IRIS. *Clin Infect Dis*. Sep 22 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26394669.

220. Fourcade C, Mauboussin JM, Lechiche C, Lavigne JP, Sotto A. Thalidomide in the treatment of immune reconstitution inflammatory syndrome in HIV patients with neurological tuberculosis. *AIDS Patient Care STDS*. Nov 2014;28(11):567-569. Available at http://www.ncbi.nlm.nih.gov/pubmed/25285462.

221. John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?' AIDS, 22 July 2005. *AIDS*. Nov 18 2005;19(17):2049-2050. Available at http://www.ncbi.nlm.nih.gov/pubmed/16260919.

222. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect*. Aug 2003;79(4):337-338. Available at http://www.ncbi.nlm.nih.gov/pubmed/12902592.

223. Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS*. Jan 2 2009;23(1):143-145. Available at http://www.ncbi.nlm.nih.gov/pubmed/19050399.

224. Chen WL, Lin YF, Tsai WC, Tsao YT. Unveiling tuberculous pyomyositis: an emerging role of immune reconstitution inflammatory syndrome. *Am J Emerg Med*. Feb 2009;27(2):251 e251-252. Available at http://www.ncbi.nlm.nih.gov/pubmed/19371548.

225. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis*. Jul 1 2003;37(1):101-112. Available at http://www.ncbi.nlm.nih.gov/pubmed/12830415.

226. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. Nov 17 2001;358(9294):1687-1693. Available at http://www.ncbi.nlm.nih.gov/pubmed/11728545.

227. Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India.

J Infect Dis. Mar 2010;201(5):691-703. Available at http://www.ncbi.nlm.nih.gov/pubmed/20121433.

228. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med*. Dec 15 2004;170(12):1360-1366. Available at http://www.ncbi.nlm.nih.gov/pubmed/15477492.
229. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD, Jr., Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. Oct 28 2000;356(9240):1470-1474. Available at http://www.ncbi.nlm.nih.gov/pubmed/11081529.
230. Haller L, Sossouhounto R, Coulibaly IM, Dosso M, al e. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. *Chemotherapy*. 1999;45(6):452-465. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10567776&query_hl=182&itool=pubmed_docsum.
231. Mofenson LM, Rodriguez EM, Hershow R, et al. Mycobacterium tuberculosis infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. *Arch Intern Med*. May 22 1995;155(10):1066-1072. Available at http://www.ncbi.nlm.nih.gov/pubmed/7748050.
232. Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. *Infect Dis Obstet Gynecol*. 1998;6(1):13-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/9678142.
233. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynaecol Obstet*. Feb 1994;44(2):119-124. Available at http://www.ncbi.nlm.nih.gov/pubmed/7911094.
234. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med*. Aug 26 1999;341(9):645-649. Available at http://www.ncbi.nlm.nih.gov/pubmed/10460815.
235. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. *J Infect Dis*. Dec 15 2010;202(12):1826-1835. Available at http://www.ncbi.nlm.nih.gov/pubmed/21067370.
236. Jonnalagadda SR, Brown E, Lohman-Payne B, et al. Consistency of Mycobacterium tuberculosis-specific interferon-gamma responses in HIV-1-infected women during pregnancy and postpartum. *Infect Dis Obstet Gynecol*. 2012;2012:950650. Available at http://www.ncbi.nlm.nih.gov/pubmed/22496602.
237. Lighter-Fisher J, Surette AM. Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol*. Jun 2012;119(6):1088-1095. Available at http://www.ncbi.nlm.nih.gov/pubmed/22569120.
238. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. Jul 2010;10(7):489-498. Available at http://www.ncbi.nlm.nih.gov/pubmed/20610331.
239. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clin Infect Dis*. Jul 15 2007;45(2):241-249. Available at http://www.ncbi.nlm.nih.gov/pubmed/17578786.
240. Middelkoop K, Bekker LG, Myer L, et al. Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township. *Am J Respir Crit Care Med*. Oct 15 2010;182(8):1080-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/20558626.
241. Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. 2013. Available at http://www.cdc.gov/tb/publications/ltbi/treatment.htm.
242. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG*. Jan 2011;118(2):226-231. Available at http://www.ncbi.nlm.nih.gov/pubmed/21083862.
243. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol* Clin North Am. Sep 1997;24(3):659-673. Available at http://www.ncbi.nlm.nih.gov/pubmed/9266585.
244. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Saf*. 2001;24(7):553-565. Available at http://www.ncbi.nlm.nih.gov/pubmed/11444726.
245. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A population-based case-control study of the safety of oral anti-

tuberculosis drug treatment during pregnancy. *Int J Tuberc Lung Dis*. Jun 2001;5(6):564-568. Available at http://www.ncbi.nlm.nih.gov/pubmed/11409585.

246. Efferen LS. Tuberculosis and pregnancy. *Curr Opin Pulm Med*. May 2007;13(3):205-211. Available at http://www.ncbi.nlm.nih.gov/pubmed/17414128.
247. Vilarinho LC. Congenital tuberculosis: a case report. *Braz J Infect Dis*. Oct 2006;10(5):368-370. Available at http://www.ncbi.nlm.nih.gov/pubmed/17293929.
248. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of Mycobacterium tuberculosis in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis*. Jan 2004;8(1):59-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/14974747.
249. Franks AL, Binkin NJ, Snider DE, Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Public Health Rep*. Mar-Apr 1989;104(2):151-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/2495549.
250. World Health Organization. Treatment of tuberculosis:guidelines for national programs. Paper presented at: WHO/TB/97.2201997; Geneva, Switzerland.
251. Enarson D, Rieder H, Arnodottir T, Trebucq A. Management of tuberculosis: a guide for low income countries. 4th ed. Paris, France: International Union Against Tuberculosis and Lung Disease; 1996.
252. Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. *Diss Pharm Pharmacol*. 1971;23:383-392.
253. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of Tuberculosis. *MMWR*. 2003;52(RR-11). Available at http://www.cdc.gov/MMWR/preview/MMWRhtml/rr5211a1.htm.
254. Shin S, Guerra D, Rich M, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. *Clin Infect Dis*. Apr 15 2003;36(8):996-1003. Available at http://www.ncbi.nlm.nih.gov/pubmed/12684912.
255. Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. *Chest*. Mar 2003;123(3):953-956. Available at http://www.ncbi.nlm.nih.gov/pubmed/12628902.
256. Drobac PC, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. *Clin Infect Dis*. Jun 1 2005;40(11):1689-1692. Available at http://www.ncbi.nlm.nih.gov/pubmed/15889370.
257. Palacios E, Dallman R, Munoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clin Infect Dis*. May 15 2009;48(10):1413-1419. Available at http://www.ncbi.nlm.nih.gov/pubmed/19361302.
258. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. Nov 1996;69(2):83-89. Available at http://www.ncbi.nlm.nih.gov/pubmed/8902438.
259. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. Jun 1998;42(6):1336-1339. Available at http://www.ncbi.nlm.nih.gov/pubmed/9624471.
260. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. May 2006;107(5):1120-1138. Available at http://www.ncbi.nlm.nih.gov/pubmed/16648419.
261. Varpela E. On the Effect Exerted by First-Line Tuberculosis Medicines on the Foetus. *Acta Tuberc Pneumol Scand*. 1964;45:53-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/14209270.
262. Fujimori H et al., The effect of tuberculostatics on the fetus: An experimental production of congenital anomaly in rats by ethionamide. Proc Congen Anom Res Assoc Jpn. 1965;5:34-35.
263. Takekoshi S. Effects of hydroxymethylpyrimidine on isoniazid- and ethionamide-induced teratosis. *Gunma J Med Sci*. 1965;14:233-244.
264. Khan I AA. Study of teratogenic activity of trifluoperazine, amitriptyline, ethionamide and thalidomide in pregnant rabbits and mice. *Proc Eur Soc Study Drug Toxic*. 1969;10:235-242.
265. Potworowska M S-EE, Szufladowica R. Treatment with ethionamide in pregnancy. *Gruzlica*. 1966;34:341-347.

Disseminated *Mycobacterium avium* Complex Disease (Last updated May 7, 2013; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.[1-3] *M. avium* is the etiologic agent in >95% of patients with AIDS who acquire disseminated MAC disease.[1,4-9] An estimated 7% to 12% of adults have been previously infected with MAC, although rates of disease vary in different geographic locations.[1,5,8,9] Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to subsequent risk of developing MAC disease.

The mode of transmission is thought to be through inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.

MAC disease typically occurs in patients with CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. The incidence of disseminated MAC disease is 20% to 40% in patients with severe AIDS-associated immunosuppression, in the absence of effective antiretroviral therapy (ART) or chemoprophylaxis.[10,11] The overall incidence of disseminated MAC disease among HIV-infected patients has fallen more than 10-fold since the introduction of effective ART, to a current level of 2.5 cases of MAC as the first opportunistic infection (OI), per 1,000 person-years, for individuals in care.[12] Factors other than a CD4 count <50 cells/mm^3 that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, previous colonization of the respiratory or gastrointestinal tract with MAC, and reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire.

Clinical Manifestations

In patients with AIDS who are not on ART, MAC disease typically is a disseminated, multi-organ infection.[13-17] Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.[5]

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels.[1,2,4-11,18,19] Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur with localized disease.

Localized manifestations of MAC disease have been reported most often in patients who are receiving and have responded to ART with an increase in CD4 T-cell counts, suggesting improved immune function. Localized syndromes include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft-tissue abscesses, genital ulcers, or central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), described below.

Initially characterized by focal lymphadenitis with fever, IRIS subsequently has been recognized as a systemic inflammatory syndrome with signs and symptoms that are clinically indistinguishable from active MAC infection. Its occurrence with MAC disease is similar to IRIS or paradoxical reactions observed with tuberculosis (TB) disease.[20-23] Bacteremia is absent. The syndrome has been described in patients with subclinical (unmasking IRIS) or established MAC disease and advanced immunosuppression who begin ART and have a rapid and marked increase in CD4 cell count (≥100 cells/mm^3). As with TB, the syndrome may be benign and self-limited or may result in severe, unremitting symptoms that improve with the use of systemic

anti-inflammatory therapy or corticosteroids in doses similar to those described for TB-associated IRIS.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids.[11,16,17,24,25] Species identification should be performed using specific DNA probes, high-performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including acid-fast bacilli smear and culture of stool or tissue biopsy material, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Preventing Exposure

MAC organisms commonly contaminate environmental sources, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Indication for Primary Prophylaxis

HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have CD4 counts <50 cells/mm^3 **(AI)**.

Preferred and Alternative Drugs for Prophylaxis

Azithromycin[26] and clarithromycin[2,27] are the preferred prophylactic agents **(AI)**. The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, associated with a higher rate of adverse effects than either drug alone, and **should not be used (AI)**.[2] The combination of azithromycin with rifabutin is more effective than azithromycin alone in preventing MAC disease.[26] However, based on the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone, this regimen **is not recommended (AI)**. Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. In patients who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC disease **(BI)**, although drug interactions may complicate use of this agent. Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which for some patients may include obtaining a blood culture for MAC. TB also should be excluded before rifabutin is used for MAC prophylaxis because treatment with the drug could result in acquired resistance to *M. tuberculosis* in patients who have active TB.

Detection of MAC organisms in the respiratory or GI tract may predict disseminated MAC infection, but no data are available regarding efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs among asymptomatic patients harboring MAC organisms at these sites in the presence of a negative blood culture. Therefore, routine screening of respiratory or GI specimens for MAC **is not recommended**.

Discontinuing Primary Prophylaxis

Primary MAC prophylaxis should be discontinued in adults and adolescents who have responded to ART with an increase in CD4 count to >100 cells/mm^3 for ≥3 months **(AI)**. Two randomized, placebo-controlled trials and observational data have demonstrated that such patients can discontinue primary prophylaxis with minimal risk of acquiring MAC disease.[28-32] Discontinuing primary prophylaxis in patients who meet these criteria is recommended to reduce pill burden, potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Primary prophylaxis should be reintroduced if the CD4 count decreases to <50 cells/mm^3 **(AIII)**.

Treating Disease

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI)**.[3,8,9,33-40] Clarithromycin is the preferred first agent **(AI)**; it has been studied more extensively than azithromycin in patients with AIDS and appears to be associated with more rapid clearance of MAC from the blood.[3,33,35,39-41] However, azithromycin can be substituted for clarithromycin when drug interactions or intolerance to clarithromycin preclude its use **(AII)**. Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.[42,43]

Ethambutol is the recommended second drug **(AI)**. Some clinicians add rifabutin as a third drug **(CI)**. One randomized clinical trial demonstrated that adding rifabutin to the combination of clarithromycin and ethambutol improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance[3,35] in individuals with AIDS and disseminated MAC disease. These studies were completed before the availability of effective ART. Whether similar results would be observed for patients receiving effective ART has not been established. The addition of a third or fourth drug should be considered in patients with advanced immunosuppression (CD4 count <50 cells/mm^3), high mycobacterial loads (>2 log_{10} colony-forming units/mL of blood), or in the absence of effective ART, settings in which mortality is increased and emergence of drug resistance is most likely **(CIII)**. On the basis of data in patients not infected with HIV, the third or fourth drug can include an injectable agent such as amikacin or streptomycin **(CIII)**, or possibly a fluoroquinolone such as levofloxacin or moxifloxacin **(CIII)**, both of which appear to have *in vitro* activity against MAC, although no randomized clinical trials have evaluated their singular efficacy in the setting of clarithromycin or azithromycin treatment or effective ART.[42]

Special Considerations with Regard to Starting ART

ART generally should be started as soon as possible after the first 2 weeks of initiating antimycobacterial therapy in patients with disseminated MAC disease who have not been treated previously with or are not receiving effective ART **(CIII)**. The rationale for starting antimycobacterial therapy first is to lower the initial pill burden and to reduce the risk of drug interactions and complications associated with IRIS that might occur should both therapies be started simultaneously **(CIII)**. The rationale for starting ART as soon as possible after the first 2 weeks of antimycobacterial therapy is to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression **(CIII)**. If ART has already been instituted, it should be continued and optimized unless drug interactions preclude safe concomitant use of antiretroviral and antimycobacterial drugs **(CIII)**. Patients will need continuous antimycobacterial treatment unless they achieve immune reconstitution via antiretroviral drugs.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy only in patients who fail to have a clinical response to their initial treatment regimens. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 to 4 weeks after initiation of appropriate therapy; clinical response may be delayed, however, in those with more extensive disease or advanced immunosuppression.

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI)**.[44] Rifabutin doses of ≥450 mg/day have been associated with higher risk of adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome P450 (CYP450) isoenzyme 3A4 and may be associated with a higher risk of experiencing uveitis, arthralgias, neutropenia, or other adverse drug reactions.[45,46]

Patients who develop moderate-to-severe symptoms typical of IRIS during ART should receive initial treatment with non-steroidal, anti-inflammatory drugs **(CIII)**. If IRIS symptoms do not improve, short-term

(4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity **(CII)**.[21,47]

Dosage adjustment with rifabutin is necessary in patients receiving protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) because of complex drug interactions.[48,49] PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made on the basis of existing data. The ability of efavirenz to induce metabolism of clarithromycin can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, the efficacy of clarithromycin for MAC prophylaxis could be reduced because of this interaction. Azithromycin metabolism is not affected by the CYP450 system; azithromycin can be used safely in the presence of PIs or NNRTIs without concerns about drug interactions.

Managing Treatment Failure

Treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for patients whose disease relapses after an initial response. Most patients who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected.[3,8,9,33,50,51]

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multidrug regimen. The regimen should consist of at least two new drugs not used previously, to which the isolate is susceptible. Drugs from which to choose are ethambutol, rifabutin, amikacin, or a fluoroquinolone (moxifloxacin, ciprofloxacin, or levofloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling **(CII)**.[8,9,34-38,41,52-56] Data in patients being treated for MAC who are HIV-uninfected indicate that an injectable agent such as amikacin or streptomycin should be considered **(CIII)**.[42] Whether continuing clarithromycin or azithromycin despite resistance provides additional benefit is unknown. Clofazimine **should not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(AI)**.[34,36,54] Anecdotal evidence exists for use of other second-line agents, such as ethionamide, thiacetazone (which is not available in the United States) and cycloserine in combination with clarithromycin and azithromycin as salvage therapy, but their role in this setting is not well defined. Optimization of ART is an important adjunct to second-line or salvage therapy for MAC disease in patients for whom initial treatment is unsuccessful or who have disease that is resistant to antimycobacterial drugs **(AIII)**.

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for routine use.

Preventing Recurrence

When to Start Secondary Prophylaxis

Adult and adolescent patients with disseminated MAC disease should continue secondary prophylaxis (chronic maintenance therapy) **(AII)** unless immune reconstitution occurs as a result of ART.[29,30]

When to Stop Secondary Prophylaxis

Patients are at low risk of recurrence of MAC when they have completed a course of ≥12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have an increase in their CD4 counts to >100 cells/mm^3 that is sustained for >6 months after ART. It is reasonable to discontinue maintenance therapy in these patients, given experience with patients who have been evaluated and inferences from more extensive data that indicate the safety of discontinuing secondary prophylaxis for other OIs **(AI)**.[30,38,57,58] Secondary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(AIII)**.

Special Considerations During Pregnancy

Chemoprophylaxis for MAC disease in pregnant women and adolescents is the same as for those who are not pregnant **(AIII)**. Because clarithromycin is associated with an increased risk of birth defects evident in certain animal studies, it **is not recommended** as the first-line agent for prophylaxis or treatment of MAC in pregnancy **(BIII)**. Two studies, each with slightly more than 100 women with first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk of spontaneous abortion was noted in one study.[59,60] Azithromycin did not produce defects in animal studies, but experience is limited with use in humans during the first trimester. Azithromycin is recommended for primary prophylaxis in pregnancy **(BIII)**. For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination **(BIII)**.

Diagnostic considerations and indications for treatment of pregnant women are the same as for women who are not pregnant. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the second agent to be combined with ethambutol for treatment of MAC disease **(BIII)**. Use of ethambutol should minimize concerns regarding drug interactions, allowing initiation of ART as soon as possible during pregnancy to decrease the risk of perinatal transmission of HIV. Pregnant women whose disease fails to respond to a primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Recommendations for Preventing and Treating Disseminated *Mycobacterium avium* Complex (MAC) Disease (page 1 of 2)

Preventing 1st Episode of Disseminated MAC Disease (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <50 cells/mm^3 after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some patients) **(AI)**

Preferred Therapy:

- Azithromycin 1200 mg PO once weekly **(AI)**, *or*
- Clarithromycin 500 mg PO BID **(AI)**, *or*
- Azithromycin 600 mg PO twice weekly **(BIII)**

Alternative Therapy:

- Rifabutin 300 mg PO daily **(BI)** (dosage adjusted may be necessary based on drug-drug interactions, please refer to Table 5 for dosing recommendation when used with ARV drugs).

Note: Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >100 cells/mm^3 for ≥3 months in response to ART **(AI)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <50 cells/mm^3 **(AIII)**

Treating Disseminated MAC Disease

Preferred Therapy:

At least 2 drugs as initial therapy to prevent or delay emergence of resistance **(AI)**

- Clarithromycin 500 mg PO twice daily **(AI)** + ethambutol 15 mg/kg PO daily **(AI)**, *or*
- Azithromycin 500–600 mg **(AII)** + ethambutol 15 mg/kg PO daily **(AI)** when drug interactions or intolerance precludes the use of clarithromycin

Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.

Recommendations for Preventing and Treating Disseminated *Mycobacterium avium* Complex (MAC) Disease (page 2 of 2)

Alternative Therapy:

Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 count <50 cells/mm^3), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**.

The 3rd or 4th drug options may include:

- Rifabutin 300 mg PO daily **(CI)** (dosage adjusted may be necessary based on drug-drug interactions), *or*
- An aminoglycoside **(CIII)** such as amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily, *or*
- A fluoroquinolone **(CIII)** such as levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Same as treatment regimens

Criteria for Discontinuing Chronic Maintenance Therapy (AII):

- Completed at least 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4+ count >100 cells/mm^3 in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 <100 cells/mm^3 **(AIII)**

Other Considerations:

- NSAIDs may be used for patients who experience moderate to severe symptoms attributed to IRIS **(CIII)**.
- If IRIS symptoms persist, a short term (4–8 weeks) of systemic corticosteroid (equivalent to 20–40 mg of prednisone) can be used **(CII)**.

Key to Acronyms: MAC = *Mycobacterium avium* Complex; CD4 = CD4 T lymphocyte; PO = orally; BID = twice daily; ARV = antiretroviral; TB = tuberculosis; CFU = colony-forming units; ART = antiretroviral therapy; IV = intravenous; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; NSAIDs = Non-steroidal anti-inflammatory drugs

References

1. Inderlied PCB. Microbiology and Minimum Inhibitory Concentration Testing for Mycobacterium avium Complex Prophylaxis. *The American journal of medicine*. 1997;102(5):2-10. Available at http://linkinghub.elsevier.com/retrieve/pii/S0002934397000375?showall=true.
2. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of Mycobacterium avium complex disease in patients with AIDS: A randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. *J Infect Dis*. Apr 2000;181(4):1289-1297. Available at http://www.ncbi.nlm.nih.gov/pubmed/10762562.
3. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. Nov 1 2003;37(9):1234-1243. Available at http://www.ncbi.nlm.nih.gov/pubmed/14557969.
4. Kemper CA, Havlir D, Bartok AE, et al. Transient bacteremia due to Mycobacterium avium complex in patients with AIDS. *J Infect Dis*. Aug 1994;170(2):488-493. Available at http://www.ncbi.nlm.nih.gov/pubmed/8035044.
5. Gordin FM, Cohn DL, Sullam PM, Schoenfelder JR, Wynne BA, Horsburgh CR, Jr. Early manifestations of disseminated Mycobacterium avium complex disease: a prospective evaluation. *J Infect Dis*. Jul 1997;176(1):126-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/9207358.
6. Benson CA, Ellner JJ. Mycobacterium avium complex infection and AIDS: advances in theory and practice. *Clin Infect Dis*. Jul 1993;17(1):7-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/8353249.
7. Havlik JA, Jr., Horsburgh CR, Jr., Metchock B, Williams PP, Fann SA, Thompson SE, 3rd. Disseminated

Mycobacterium avium complex infection: clinical identification and epidemiologic trends. *J Infect Dis*. Mar 1992;165(3):577-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/1347060.

8. Benson CA. Treatment of disseminated disease due to the Mycobacterium avium complex in patients with AIDS. *Clin Infect Dis*. Apr 1994;18 Suppl 3:S237-242. Available at http://www.ncbi.nlm.nih.gov/pubmed/8204776.
9. Benson CA. Disease due to the Mycobacterium avium complex in patients with AIDS: epidemiology and clinical syndrome. *Clin Infect Dis*. Apr 1994;18 Suppl 3:S218-222. Available at http://www.ncbi.nlm.nih.gov/pubmed/8204773.
10. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. *J Infect Dis*. Jun 1992;165(6):1082-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/1349906.
11. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T. Incidence and natural history of Mycobacterium avium-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *The American review of respiratory disease*. Aug 1992;146(2):285-289. Available at http://www.ncbi.nlm.nih.gov/pubmed/1362634.
12. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. Jun 19 2010;24(10):1549-1559. Available at http://www.ncbi.nlm.nih.gov/pubmed/20502317.
13. Barbaro DJ, Orcutt VL, Coldiron BM. Mycobacterium avium-Mycobacterium intracellulare infection limited to the skin and lymph nodes in patients with AIDS. *Reviews of infectious diseases*. Jul-Aug 1989;11(4):625-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/2772468.
14. Hellyer TJ, Brown IN, Taylor MB, Allen BW, Easmon CS. Gastro-intestinal involvement in Mycobacterium avium-intracellulare infection of patients with HIV. *J Infect*. Jan 1993;26(1):55-66. Available at http://www.ncbi.nlm.nih.gov/pubmed/8454889.
15. Torriani FJ, McCutchan JA, Bozzette SA, Grafe MR, Havlir DV. Autopsy findings in AIDS patients with Mycobacterium avium complex bacteremia. *J Infect Dis*. Dec 1994;170(6):1601-1605. Available at http://www.ncbi.nlm.nih.gov/pubmed/7996004.
16. Roth RI, Owen RL, Keren DF, Volberding PA. Intestinal infection with Mycobacterium avium in acquired immune deficiency syndrome (AIDS). Histological and clinical comparison with Whipple's disease. *Digestive diseases and sciences*. May 1985;30(5):497-504. Available at http://www.ncbi.nlm.nih.gov/pubmed/2580679.
17. Gillin JS, Urmacher C, West R, Shike M. Disseminated Mycobacterium avium-intracellulare infection in acquired immunodeficiency syndrome mimicking Whipple's disease. *Gastroenterology*. Nov 1983;85(5):1187-1191. Available at http://www.ncbi.nlm.nih.gov/pubmed/6194041.
18. Inderlied CB, Kemper CA, Bermudez LE. The Mycobacterium avium complex. *Clin Microbiol Rev*. Jul 1993;6(3):266-310. Available at http://www.ncbi.nlm.nih.gov/pubmed/8358707.
19. Packer SJ, Cesario T, Williams JH, Jr. Mycobacterium avium complex infection presenting as endobronchial lesions in immunosuppressed patients. *Ann Intern Med*. Sep 1 1988;109(5):389-393. Available at http://www.ncbi.nlm.nih.gov/pubmed/3165608.
20. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr Hum Retrovirol*. Feb 1 1999;20(2):122-128. Available at http://www.ncbi.nlm.nih.gov/pubmed/10048898.
21. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. Nov 15 2005;41(10):1483-1497. Available at http://www.ncbi.nlm.nih.gov/pubmed/16231262.
22. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. Jan 24 1998;351(9098):252-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/9457095.
23. Cabie A, Abel S, Brebion A, Desbois N, Sobesky G. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis*. Nov 1998;17(11):812-813. Available at http://www.ncbi.nlm.nih.gov/pubmed/9923530.
24. Shanson DC, Dryden MS. Comparison of methods for isolating Mycobacterium avium-intracellulare from blood of patients with AIDS. *J Clin Pathol*. Jun 1988;41(6):687-690. Available at http://www.ncbi.nlm.nih.gov/pubmed/3385000.

25. Hafner R, Inderlied CB, Peterson DM, et al. Correlation of quantitative bone marrow and blood cultures in AIDS patients with disseminated Mycobacterium avium complex infection. *J Infect Dis*. Aug 1999;180(2):438-447. Available at http://www.ncbi.nlm.nih.gov/pubmed/10395860.

26. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. Aug 8 1996;335(6):392-398. Available at http://www.ncbi.nlm.nih.gov/pubmed/8676932.

27. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated Mycobacterium avium complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med*. Aug 8 1996;335(6):384-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/8663871.

28. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/10915098.

29. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for Mycobacterium avium complex disease in HIV-infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. Apr 13 2000;342(15):1085-1092. Available at http://www.ncbi.nlm.nih.gov/pubmed/10766581.

30. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of Mycobacterium avium complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med*. Oct 3 2000;133(7):493-503. Available at http://www.ncbi.nlm.nih.gov/pubmed/11015162.

31. Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against Mycobacterium avium in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS*. Jul 7 2000;14(10):1409-1412. Available at http://www.ncbi.nlm.nih.gov/pubmed/10930156.

32. Brooks JT, Song R, Hanson DL, et al. Discontinuation of primary prophylaxis against Mycobacterium avium complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992-2002. *Clin Infect Dis*. Aug 15 2005;41(4):549-553. Available at http://www.ncbi.nlm.nih.gov/pubmed/16028167.

33. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic Mycobacterium avium complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med*. Dec 15 1994;121(12):905-911. Available at http://www.ncbi.nlm.nih.gov/pubmed/7978715.

34. May T, Brel F, Beuscart C, et al. Comparison of combination therapy regimens for treatment of human immunodeficiency virus-infected patients with disseminated bacteremia due to Mycobacterium avium. ANRS Trial 033 Curavium Group. Agence Nationale de Recherche sur le Sida. *Clin Infect Dis*. Sep 1997;25(3):621-629. Available at http://www.ncbi.nlm.nih.gov/pubmed/9314450.

35. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with Mycobacterium avium complex. *Clin Infect Dis*. May 1999;28(5):1080-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452638.

36. Dube MP, Sattler FR, Torriani FJ, et al. A randomized evaluation of ethambutol for prevention of relapse and drug resistance during treatment of Mycobacterium avium complex bacteremia with clarithromycin-based combination therapy. California Collaborative Treatment Group. *J Infect Dis*. Nov 1997;176(5):1225-1232. Available at http://www.ncbi.nlm.nih.gov/pubmed/9359722.

37. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated Mycobacterium avium complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Terry Beirn Community Programs for Clinical Research on AIDS. *Clin Infect Dis*. Jul 1999;29(1):125-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/10433575.

38. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated mycobacterium avium complex infection after 12 months of antimycobacterial therapy combined with highly active antiretroviral therapy. *J Infect Dis*. Nov 1998;178(5):1446-1449. Available at http://www.ncbi.nlm.nih.gov/pubmed/9780266.

39. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. *Clin Infect Dis*. Nov 1998;27(5):1278-1285. Available at http://www.ncbi.nlm.nih.gov/pubmed/9827282.

40. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with human immunodeficiency virus. *Clin Infect Dis*. Nov 2000;31(5):1245-1252. Available at http://www.ncbi.nlm.nih.gov/pubmed/11073759.

41. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. *N Engl J Med*. Aug 8 1996;335(6):377-383. Available at http://www.ncbi.nlm.nih.gov/pubmed/8676931.

42. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. Feb 15 2007;175(4):367-416. Available at http://www.ncbi.nlm.nih.gov/pubmed/17277290.

43. Gardner EM, Burman WJ, DeGroote MA, Hildred G, Pace NR. Conventional and molecular epidemiology of macrolide resistance among new Mycobacterium avium complex isolates recovered from HIV-infected patients. *Clin Infect Dis*. Oct 1 2005;41(7):1041-1044. Available at http://www.ncbi.nlm.nih.gov/pubmed/16142672.

44. Abbot Laboratories. clarithromycin (biaxin). Abbot Park, IL: Abbot Laboratories; 1995.

45. Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. MAC Study Group of the Canadian HIV Trials Network. *N Engl J Med*. Feb 10 1994;330(6):438-439. Available at http://www.ncbi.nlm.nih.gov/pubmed/8284019.

46. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother*. Mar 1998;42(3):631-639. Available at http://www.ncbi.nlm.nih.gov/pubmed/9517944.

47. Wormser GP, Horowitz H, Dworkin B. Low-dose dexamethasone as adjunctive therapy for disseminated Mycobacterium avium complex infections in AIDS patients. *Antimicrob Agents Chemother*. Sep 1994;38(9):2215-2217. Available at http://www.ncbi.nlm.nih.gov/pubmed/7811052.

48. TB/HIV Drug Interactions. www.cdc.gov/tb_HIV_Drugs/Rifabutin.htm.

49. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on March 4, 2013.

50. Heifets L, Lindholm LP, Libonati J. Radiometric broth macrodilution method for determination of minimal inhibitory concentrations(MIC) with Mycobacterium avium complex isolates: proposed guidelines. Paper presented at: national Jewish Center for Immunology and Respiratory Medicine. 1993.

51. Heifets L, Mor N, Vanderkolk J. Mycobacterium avium strains resistant to clarithromycin and azithromycin. *Antimicrob Agents Chemother*. Nov 1993;37(11):2364-2370. Available at http://www.ncbi.nlm.nih.gov/pubmed/8031351.

52. Masur H. Recommendations on prophylaxis and therapy for disseminated Mycobacterium avium complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for Mycobacterium avium Complex. *N Engl J Med*. Sep 16 1993;329(12):898-904. Available at http://www.ncbi.nlm.nih.gov/pubmed/8395019.

53. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of Mycobacterium avium complex bacteremia in AIDS with a four-drug oral regimen. Rifampin, ethambutol, clofazimine, and ciprofloxacin. The California Collaborative Treatment Group. *Ann Intern Med*. Mar 15 1992;116(6):466-472. Available at http://www.ncbi.nlm.nih.gov/pubmed/1739237.

54. Chaisson RE, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic Mycobacterium avium complex disease in patients with HIV infection. *AIDS*. Mar 1997;11(3):311-317. Available at http://www.ncbi.nlm.nih.gov/pubmed/9147422.

55. Chiu J, Nussbaum J, Bozzette S, et al. Treatment of disseminated Mycobacterium avium complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. California Collaborative Treatment Group. *Ann Intern Med*. Sep 1 1990;113(5):358-361. Available at http://www.ncbi.nlm.nih.gov/pubmed/2382918.

56. Rodriguez Diaz JC, Lopez M, Ruiz M, Royo G. In vitro activity of new fluoroquinolones and linezolid against non-tuberculous mycobacteria. *International journal of antimicrobial agents*. Jun 2003;21(6):585-588. Available at http://www.ncbi.nlm.nih.gov/pubmed/12791475.

57. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community

Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. Dec 24 1998;339(26):1889-1895. Available at http://www.ncbi.nlm.nih.gov/pubmed/9862944.

58. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated Mycobacterium avium complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis*. Apr 1 2003;187(7):1046-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/12660918.

59. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *American journal of perinatology*. 1998;15(9):523-525. Available at http://www.ncbi.nlm.nih.gov/pubmed/9890248.

60. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiology and drug safety*. Dec 2000;9(7):549-556. Available at http://www.ncbi.nlm.nih.gov/pubmed/11338912.

Bacterial Respiratory Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Bacterial respiratory diseases; including sinusitis, bronchitis, otitis, and pneumonia; are among the most common infectious complications in patients with HIV infection, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts,[1] and some data suggest that bacterial pneumonia may occur with increased severity in this population. This chapter will focus on the diagnosis, prevention, and management of bacterial pneumonia in HIV-infected patients.

Bacterial pneumonia is a common cause of HIV-associated morbidity and recurrent pneumonia (2 or more episodes within a 1-year period) is an AIDS-defining condition. The incidence of bacterial pneumonia is higher in HIV-infected individuals than in those who are not HIV infected.[2] More recently, the incidence of bacterial pneumonia in HIV-infected individuals has declined. In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years in the era before combination antiretroviral therapy (ART) to 9.1 episodes per 100 person-years by 1997.[3-5]

Bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4 count. The high rates of bacterial pneumonia in HIV-infected individuals probably result from multiple factors, including qualitative B-cell defects that impair ability to produce pathogen-specific antibody; impaired neutrophil function or numbers, or both; and factors, such as injection drug use, that are associated with underlying HIV infection. Risk factors associated with an increased risk of bacterial pneumonia include low CD4 count (< 200 cells/mm^3), no or intermittent use of ART, cigarette smoking, injection drug use, and chronic viral hepatitis.

In HIV-infected individuals, as in those who are not HIV infected, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia.[6-12] Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila* species have been reported as infrequent causes of community-acquired bacterial pneumonia in HIV-infected individuals.[9,13]

The frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* as community-acquired pathogens is higher in HIV-infected individuals than in those not HIV infected.[10,14] Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, in particular, should be considered as a potential etiology for pneumonia, given that community outbreaks of MRSA have been seen in men who have sex with men and nasal carriage of MRSA is more common in HIV-infected individuals, particularly at lower CD4 cell counts.[15] Also, community-acquired MRSA pneumonia may not invariably be associated with preceding influenza illness.[16]

In HIV-infected patients, particularly those infected with *S. pneumoniae*, incidence of bacteremia accompanying pneumonia is increased compared with that in individuals who are not HIV infected. In one study, the estimated rate of pneumococcal bacteremia in patients with AIDS (1,094 cases per 100,000) was ~55 times that in HIV-uninfected individuals (20 cases per 100,000). This disparity narrowed but was not eliminated after the introduction of ART.[17] Other studies have highlighted the declining incidence of pneumococcal bacteremia in the era of ART.[18]

Bacterial pneumonia is associated with increased mortality in HIV-infected individuals.[10,19,20] In HIV-infected individuals with community-acquired bacterial pneumonia, a prospective, multicenter study documented CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock as independent predictors of increased mortality.[21] In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline radiograph all were independent predictors of radiographic progression of disease.

Clinical Manifestations

Clinical and radiographic presentation of bacterial pneumonia in HIV-infected individuals is similar to that in those who are not HIV infected. Patients with pneumonias caused by bacteria such as *S. pneumoniae* or *Haemophilus* species characteristically have acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea.[22] They are often febrile and the presence of fever, tachycardia, or hypotension can be an indicator of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia and clinicians should strongly consider hospitalizing such patients.

Patients with bacterial pneumonia typically have signs of focal consolidation, such as egophony, and/or pleural effusion on lung examination. In contrast, lung examination often is normal in those with *Pneumocystis* pneumonia (PCP), and if abnormal, reveals inspiratory crackles. In patients with bacterial pneumonia, the white blood cell (WBC) count usually is elevated. The elevation may be relative to baseline WBC in those with advanced HIV. A left shift in WBC differential may be present.

Individuals with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to *S. pneumoniae* or *Haemophilus* typically present with consolidation, whereas presence of cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for those with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. Criteria developed to assess disease severity in HIV-uninfected persons, such as the Pneumonia Severity Index (PSI) (http://pda.ahrq.gov/clinic/psi/psicalc.asp) appear to be valid for HIV-infected patients, especially when used in combination with CD4 count[21,23] (discussed in further detail in Treating Disease).

Diagnosis

Guidelines for diagnosing and managing community-acquired pneumonia (CAP) in individuals who are not HIV infected also apply to those who are infected.[24] Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs, if possible. If previous radiographs are available, they should be reviewed to assess for presence of new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate.

Given the increased incidence of *Mycobacterium tuberculosis* in HIV-infected individuals, a tuberculosis (TB) diagnosis should always be considered in HIV-infected patients who have pneumonia. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (that is, with respiratory isolation if hospitalized), and two to three sputum specimens should be obtained for acid fast bacilli evaluation. In settings where the prevalence of TB is high, initiation of empiric therapy for both bacterial pneumonia and TB may be appropriate for patients in whom both diagnoses are strong considerations and after diagnostic studies are undertaken.

Often, the differential diagnosis of pneumonia in HIV-infected individuals is broad and a confirmed microbiologic diagnosis allows clinicians to target the specific pathogen and discontinue broad spectrum antibiotic therapy and/or empiric therapy (such as empiric PCP therapy) that targets non-bacterial pathogens.

HIV-infected patients with suspected CAP should undergo investigation for specific pathogens that would significantly alter standard (empirical) management decisions when presence of such pathogens is suspected based on epidemiologic, clinical, or radiologic clues. *P. aeruginosa* should be considered in HIV-infected patients with advanced HIV disease (that is, CD4 count $\leq$50 cells/mm^3), pre-existing lung disease such as

bronchiectasis, or underlying neutropenia. It is also a consideration for HIV-infected patients who use corticosteroids, are severely malnourished, have been hospitalized in the past 90 days or reside in a health care facility or nursing home, or are on chronic hemodialysis. Because cavitary infiltrates are common in patients with *P. aeruginosa*, that radiographic finding also should prompt an investigation for this pathogen. *S. aureus* should be considered in patients with recent viral (or influenza) infection; a history of injection drug use; or severe, bilateral, necrotizing pneumonia.

Routine diagnostic tests to identify an etiologic diagnosis are optional for HIV-infected patients with suspected CAP who are well enough to be treated as outpatients, especially if the microbiologic studies cannot be performed promptly.

In contrast, a pre-treatment expectorated sputum specimen for Gram stain and culture and two blood cultures should be obtained from HIV-infected patients hospitalized for suspected CAP, particularly those who require intensive care.

Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures can be met for collection, transport, and processing of samples. Correlation of sputum culture with Gram stain can help in interpretation of sputum culture data. For intubated patients, an endotracheal aspirate sample should be obtained. Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis is broad and includes pathogens such as *Pneumocystis jirovecii*.

The increased incidence of bacteremia in HIV-infected patients, especially those with low CD4 cell counts, and the high specificity of blood cultures argue for their collection in such individuals. Low sensitivity of blood cultures in persons with higher CD4 counts argues against routine collection. However, patients with HIV infection are at increased risk of infection with drug-resistant pneumococci.[25,26] Because identification of this organism could lead to changes in management, collection of blood specimens in HIV-infected patients with CAP should always be considered.

In addition to the above tests, urinary antigen tests for *L. pneumophila* and *S. pneumoniae* should be considered.

Diagnostic thoracentesis should be considered in all patients with pleural effusion, especially if concern exists for accompanying empyema, and therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion.

Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community.

Preventing Disease

Vaccination against *S. pneumoniae* and influenza, use of combination ART, and lifestyle modifications are all important measures in preventing bacterial pneumonia. Multiple observational studies of pneumococcal polysaccharide vaccine (PPV) in the United States have reported benefits from such vaccination in HIV-infected persons.[27-32] Several studies also have documented an association between vaccination and a reduced risk of pneumococcal bacteremia.[18,32] One randomized placebo-controlled trial of PPV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia.[33] Follow-up of this cohort confirmed the increase in pneumonia in vaccinated subjects but also showed a decrease in all-cause mortality.[34]

A 13-valent pneumococcal conjugate vaccine (PCV13) has recently been recommended by the Advisory Committee on Immunization Practices for use in adults with immunocompromising conditions, including HIV infection.[35] A randomized, double-blind, placebo-controlled trial of 7-valent PCV among HIV-infected

adults in Malawi demonstrated 74% efficacy against vaccine-type invasive pneumococcal disease, with clear evidence of efficacy in those with CD4 counts <200 cells/mm^3.[36]

HIV-infected adults and adolescents who have never received any pneumococcal vaccine should receive a single dose of PCV13 regardless of CD4 count **(AI)**.[35] Patients with CD4 counts ≥200 cells/mm^3 should then receive a dose of 23-valent PPV (PPV23) at least 8 weeks later **(AII)**.[27-32,37-39] HIV-infected patients with CD4 counts <200 cells/mm^3 can be offered PPV23 at least 8 weeks after receiving PCV13 **(CIII)**; however, it may be preferable to defer PPV23 until after the CD4 count increases to >200 cells/mm^3 on ART **(BIII)**. Clinical evidence supporting use of PPV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL;[37,39] evidence also suggests benefit for those who start ART before receiving PPV.[32]

The duration of the protective effect of PPV23 is unknown; a single revaccination with PPV is recommended if ≥5 years have elapsed since the first dose of PPV23 was given **(BIII)**.[31] A third dose of PPV23 should be given at age 65 years or later, as long as 5 years have elapsed since the most recent dose and it was given before age 65 years **(BIII)**.

PCV13 should also be given in HIV-infected patients who have already received PPV23 **(AII)**. However, such patients should wait at least 1 year after their most recent dose of PPV23 before receiving a single dose of PCV13 **(BIII)**.[35] Subsequent doses of PPV23 should be given according to the schedule outlined above (i.e., at least 5 years between doses of PPV23 with no more than 3 lifetime doses).

Inactivated influenza vaccine should be administered annually during influenza season to all HIV-infected individuals **(AIII)**.[40] This recommendation is pertinent to prevention of bacterial pneumonia, which can occur as a complication of influenza. Use of live attenuated influenza vaccine is contraindicated and **is not recommended** in HIV-infected individuals **(AIII)**.

The incidence of *H. influenzae* type b infection in HIV-infected adults is low. Therefore, *H. influenzae* type vaccine **is not usually recommended** for adult use **(BIII)** unless a patient also has anatomic or functional asplenia.

Several factors are associated with a decreased risk of bacterial pneumonia, including use of ART and of trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.[20] In many studies, daily administration of TMP-SMX for PCP prophylaxis also reduced the frequency of bacterial respiratory infections.[2,41,42] This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of this drug (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(BIII)**. Similarly, clarithromycin administered daily and azithromycin administered weekly are the drugs of choice for *Mycobacterium avium* complex (MAC) prophylaxis and may be effective in preventing bacterial respiratory infections.[43,44] However, these drugs also should not be prescribed solely for preventing bacterial respiratory infection **(BIII)**.

A decreased absolute neutrophil count (e.g., <500 cells/mm^3) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignancies. To reduce the risk of such bacterial infections, clinicians can consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs **(CIII)** or by administering granulocyte-colony stimulating factor **(CIII)**, although these interventions have not been demonstrated to be effective in HIV-infected persons.

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes and using injection drugs and alcohol.[2,38,45-47] Clinicians should encourage cessation of these behaviors, and data suggest that smoking cessation can decrease the risk of bacterial pneumonia.[48]

Treating Disease

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. One study suggested that the site of care decision be dictated by considering the PSI and CD4 count together.[23] Mortality was increased in patients with higher PSI class, but even in those without an increased mortality risk by PSI, the presence of a CD4 count <200 cells/mm^3 was associated with an increased risk of death.[23] This led to the suggestion to always offer hospitalization to CAP patients with CD4 counts <200 cells/mm^3 and to use the PSI to help guide the decision in those with higher CD4 counts.[49] In fact, in one series of 118 HIV-infected patients with CAP who were hospitalized, 62% fell into PSI Classes I and II, groups that are rarely hospitalized if not HIV infected.[50] In another study, 40% of hospitalized HIV-infected patients in low-risk PSI classes had CD4 counts <200 cells/mm^3.[23]

The basic principles of treatment of community-acquired bacterial pneumonia are the same for HIV-infected patients as for those who are not HIV infected.[24] As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should be taken before antibiotic therapy is initiated. Antibiotic therapy should be administered promptly, however, without waiting for the results of diagnostic testing.

Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases

Outpatient Treatment

HIV-infected individuals who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide **(AII)** or an oral respiratory fluoroquinolone **(AII)**. Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Doxycycline is an alternative to the macrolide **(CIII)**. Preferred oral respiratory fluoroquinolones are moxifloxacin or levofloxacin.

An oral respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used in patients who are allergic to penicillin **(AII)**.

Respiratory fluoroquinolones also are active against *M. tuberculosis*. Thus, patients with TB who are treated with fluoroquinolone monotherapy may have an initial but misleading response that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy and increase risk of drug-resistant TB and TB transmission. Fluoroquinolones, therefore, should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy. Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be routinely recommended (BIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

Non-Intensive Care Unit Inpatient Treatment

HIV-infected individuals who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide **(AII)** or an IV respiratory fluoroquinolone **(AII)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Doxycycline is an alternative to the macrolide **(CIII)**. Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. Clinical and Laboratory Standards Institute and U.S. Food and Drug Administration changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply that clinicians can consider treatment with IV penicillin in HIV-infected patients confirmed to have pneumococcal pneumonia **(BIII)**.[51]

In patients who are allergic to penicillin, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(AII)**.

Because of the activity of fluoroquinolones against *M. tuberculosis* and the dangers of monotherapy in those with TB, as previously discussed, fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy.

Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be recommended routinely (BIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

Intensive Care Unit Treatment

Intensive care unit patients should not receive empiric monotherapy, even with a fluoroquinolone, because the efficacy of this approach has not been established. In one study, the use of dual therapy (usually with a beta-lactam plus a macrolide) was associated with reduced mortality in patients with bacteremic pneumococcal pneumonia, including those admitted to the intensive care unit.[52] Patients with severe pneumonia who require intensive care should be treated with an IV beta-lactam plus either IV azithromycin **(AII)** or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AII)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam.

In patients who are allergic to penicillin, aztreonam plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(BIII)**.

The majority of CAP pathogens can be treated adequately with recommended empiric regimens. The increased incidence of *P. aeruginosa* and *S. aureus* (including community-acquired MRSA) as causes of CAP are exceptions. Both of these pathogens occur in specific epidemiologic patterns with distinct clinical presentations, for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative.

Empiric Pseudomonas aeruginosa Treatment

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750-mg dose) should be used **(BIII)**. Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternatives are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin **(BIII)** or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone **(BIII)**. In patients who are allergic to penicillin, aztreonam can be used in place of the beta-lactam **(BIII)**.

Empiric Staphylococcus aureus Treatment

In patients who have risk factors for *S. aureus* infection, including community-acquired MRSA, vancomycin or linezolid should be added to the antibiotic regimen **(BIII)**. Although not routinely recommended, the addition of clindamycin (to vancomycin, but not to linezolid) may be considered if severe necrotizing pneumonia is present to minimize bacterial toxin production **(CIII)**.

Pathogen-Directed Therapy

When the etiology of the pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be modified and directed at that pathogen.

Switch from Intravenous to Oral Therapy

A switch to oral therapy should be considered in patients with CAP on IV antibiotic therapy who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function. Suggested criteria for clinical stability include oral temperature <37.8°C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure ≥90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood (PaO_2) >60 mm Hg.[24]

Special Considerations Regarding When to Start Antiretroviral Therapy

The presence of acute opportunistic infection (OI), including bacterial pneumonia, increases the urgency of

starting ART. In one randomized, controlled trial, use of ART early in the course of OIs, including bacterial infections, led to less AIDS progression and death compared with later onset of therapy.[53] Therefore, in patients not already on ART, ART should be initiated early in the course of bacterial pneumonia **(AI)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

The clinical response to appropriate antimicrobial therapy is similar in HIV-infected patients and individuals who are not HIV infected.[54] A clinical response (i.e., reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) typically is observed within 48 to 72 hours after initiation of appropriate antimicrobial therapy. The presence of advanced HIV infection, CD4 count <100 cells/mm^3, and *S. pneumoniae* etiology were predictors of needing >7 days to reach clinical stability, whereas those patients receiving ART tended to become clinically stable sooner.[49] Usually, radiographic improvement lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with bacterial respiratory disease and treatment with ART in HIV-infected patients.

Managing Treatment Failure

Patients who fail to respond to appropriate antimicrobial therapy should undergo further evaluation to search for other infectious and noninfectious causes of pulmonary dysfunction. The possibility of TB should always be considered in HIV-infected patients with pulmonary disease.

Preventing Recurrence

HIV-infected patients should receive pneumococcal and influenza vaccine as recommended. Antibiotic chemoprophylaxis generally is not recommended specifically to prevent recurrences of bacterial respiratory infections because of the potential for development of drug-resistant microorganisms and drug toxicity.

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory tract infections in pregnant women is the same as in those who are not pregnant, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tract infections should be managed as in women who are not pregnant, with certain exceptions. Clarithromycin is not recommended as the first-line agent among macrolides because of an increased risk of birth defects seen in some animal studies. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk of spontaneous abortion was noted in one study.[55,56] Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy **(BIII)**. Arthropathy has been noted in immature animals with in utero exposure to quinolones. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[57,58] Thus, when indicated, quinolones can be used in pregnancy for serious respiratory infections **(CIII)**.[59]

Doxycycline is not recommended for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Pneumonia during pregnancy is associated with increased rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions **(BII)**.

Pneumococcal vaccine can be administered during pregnancy **(AIII)**. Although its safety during the first

trimester has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Inactivated influenza vaccine also can be administered during pregnancy, and the vaccine is recommended for all pregnant women during influenza season **(AIII)**. Live attenuated influenza vaccine should not be used in HIV-infected persons **(AIII)**. Because administration of vaccines can be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk of perinatal transmission of HIV.

Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 1 of 3)

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination:

- All HIV-infected persons regardless of CD4 count

Vaccination Recommendations:

For Individuals Who Have Not Received Any Pneumococcal Vaccination:

Preferred Vaccination:

- One dose of PCV13 **(AI)**, followed by:
- For patients with CD4+ count ≥200 cells/μL: PPV23 should be given at least 8 weeks after receiving PCV13 **(AII)**; *or*
- For patients with CD4 count <200 cells/μL: PPV23 can be offered at least 8 weeks after receiving PCV13 **(CIII)** or can await increase of CD4 count to >200 cells/μL on ART **(BIII)**

Alternative Vaccination:

- One dose of PPV23 **(BII)**

For Individuals Who Have Previously Received PPV23:

- One dose of PCV13 should be given at least 1 year after the last receipt of PPV23 **(AII)**

Re-vaccination of PPV

- A dose of PPV23 is recommended for individuals 19–64 years old if ≥5 years have elapsed since the first dose of PPV **(BIII)**
- Another dose should be given for individuals 65 years or older, if at least 5 years have elapsed since previous PPV23 dose **(BIII)**

Vaccine Dosing:

- PCV13 - 0.5 mL IM
- PPV23 - 0.5 mL IM

Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza

Indication for Influenza Vaccination:

- All HIV-infected persons during influenza season **(AIII)**

Vaccination:

- Inactivated influenza vaccine per recommendation of the season **(AIII)**

Note: Live attenuated influenza vaccine is **contraindicated** in HIV-infected persons **(AIII)**

Treating Community-Acquired Bacterial Pneumonia

Note—Empiric antimicrobial therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed below are suggested empiric therapy. The regimen should be modified as needed once microbiologic and drug susceptibility results are available.

Empiric Outpatient Therapy (Oral)

Preferred Therapy:

- An oral beta-lactam + a macrolide (azithromycin or clarithromycin) **(AII)**, *or*
    - *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
    - *Alternative beta-lactams:* cefpodoxime or cefuroxime

- A fluoroquinolone[a] **(AII)**, especially for patients with penicillin allergies
  - Levofloxacin[a] 750 mg PO once daily **(AII)**, *or*
  - Moxifloxacin[a] 400 mg PO once daily **(AII)**

Alternative Therapy:

- A beta-lactam **(AII)** + doxycycline **(CIII)**

Duration of Therapy:

- For most patients: 7–10 days; a minimum of 5 days. The patient should be afebrile for 48–72 hours, and should be clinically stable before discontinuation of therapy

Empiric Therapy for Non-ICU Hospitalized Patients

Preferred Therapy:

- An IV beta-lactam + a macrolide (azithromycin or clarithromycin) **(AII)**, *or*
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
- An IV fluoroquinolone[a] **(AII)**, especially for patients with penicillin allergies
  - Levofloxacin[a] 750 mg IV once daily **(AII)**, *or*
  - Moxifloxacin[a] 400 mg IV once daily **(AII)**

Alternative Therapy:

- An IV beta-lactam **(AII)** + doxycycline **(CIII)**
- IV penicillin may be used for confirmed pneumococcal pneumonia **(BIII)**

Empiric Therapy for ICU Patients

Preferred Therapy:

- An IV beta-lactam + IV azithromycin **(AII)**, *or*
- An IV beta-lactam + (levofloxacin[a] IV 750 mg once daily or moxifloxacin[a] 400mg IV daily) **(AII)**
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy:

For Penicillin-Allergic Patients:

- Aztreonam (IV) + an IV respiratory fluoroquinolone (moxifloxacin 400 mg per day or levofloxacin 750 mg per day) **(BIII)**

Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia

Preferred Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin IV [400 mg q8–12h] or levofloxacin IV 750 mg/day) **(BIII)**
  - *Preferred beta-lactams:* piperacillin-tazobactam, cefepime, imipenem, or meropenem

Alternative Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + IV azithromycin **(BIII)**, *or*
- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + an IV antipneumococcal fluoroquinolone (moxifloxacin [400 mg/day] or levofloxacin [750 mg/day]) **(BIII)**

For Penicillin-Allergic Patients:

- Replace the beta-lactam with aztreonam **(BIII)**

Empiric Therapy for Patients at Risk of Staphylococcus aureus Pneumonia:

- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen **(BIII)**.
- Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) may be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CIII)**.

Other Considerations

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance **(BIII)**.
- Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 3 of 3)

- Once the pathogen has been identified by reliable microbiologic methods, antibiotics should be modified to treat the pathogen **(BIII)**.
- For patients begun on IV antibiotic therapy, switching to PO should be considered when patient is clinically improved and able to tolerate oral medications.
- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities.

[a] Respiratory fluoroquinolones such as levofloxacin or moxifloxacin are also active against *Mycobacterium tuberculosis*. In patients with undiagnosed TB, fluoroquinolones may alter response to therapy, delay TB diagnosis, and increase the risk of drug resistance. These drugs should be used with caution in patients in whom TB is suspected but who are not receiving a standard 4-drug TB regimen.

Key to Acronyms: PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; CD4 = CD4 T lymphocyte cell; PPV 23 = 23-Valent Pneumococcal Polysaccharide Vaccine; ART = antiretroviral therapy; IM = intramuscularly; PO = Orally; IV = Intravenously; MAC = *Mycobacterium avium* complex

References

1. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. Jan 1997;155(1):72-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/9001292.
2. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. Sep 28 1995;333(13):845-851. Available at http://www.ncbi.nlm.nih.gov/pubmed/7651475.
3. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR. CDC surveillance summaries: Morbidity and mortality weekly report. CDC surveillance summaries / Centers for Disease Control*. Apr 16 1999;48(2):1-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/12412613.
4. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med*. Jul 2000;162(1):64-67. Available at http://www.ncbi.nlm.nih.gov/pubmed/10903221.
5. Serraino D, Puro V, Boumis E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS*. Sep 26 2003;17(14):2109-2116. Available at http://www.ncbi.nlm.nih.gov/pubmed/14502014.
6. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. Jan 1986;104(1):38-41. Available at http://www.ncbi.nlm.nih.gov/pubmed/3484420.
7. Burack JH, Hahn JA, Saint-Maurice D, Jacobson MA. Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection. Implications for rational empiric antibiotic therapy. *Arch Intern Med*. 1994;154(22):2589-2596. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7979856&query_hl=62&itool=pubmed_DocSum.
8. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax*. Apr 1994;49(4):367-368. Available at http://www.ncbi.nlm.nih.gov/pubmed/8202910.
9. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med*. Oct 1995;152(4 Pt 1):1309-1315. Available at http://www.ncbi.nlm.nih.gov/pubmed/7551387.
10. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. *Chest*. Apr 2000;117(4):1017-1022. Available at http://www.ncbi.nlm.nih.gov/pubmed/10767233.
11. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. *J Infect Dis*. Aug 1 2001;184(3):268-277. Available at http://www.ncbi.nlm.nih.gov/pubmed/11443551.

12. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. Jan 4 2002;16(1):85-95. Available at http://www.ncbi.nlm.nih.gov/pubmed/11741166.

13. Tarp B, Jensen JS, Ostergaard L, Andersen PL. Search for agents causing atypical pneumonia in HIV-positive patients by inhibitor-controlled PCR assays. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. Jan 1999;13(1):175-179. Available at http://www.ncbi.nlm.nih.gov/pubmed/10836344.

14. Levine SJ, White DA, Fels AO. The incidence and significance of Staphylococcus aureus in respiratory cultures from patients infected with the human immunodeficiency virus. *The American review of respiratory disease*. Jan 1990;141(1):89-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/2297190.

15. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant Staphylococcus aureus clone USA300 in men who have sex with men. *Annals of internal medicine*. Feb 19 2008;148(4):249-257. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18283202.

16. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant Staphylococcus aureus pneumonia. *Chest*. Jul 2010;138(1):130-136. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20173050.

17. Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. *J Infect Dis*. Jun 15 2005;191(12):2038-2045. Available at http://www.ncbi.nlm.nih.gov/pubmed/15897989.

18. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med*. Jul 11 2005;165(13):1533-1540. Available at http://www.ncbi.nlm.nih.gov/pubmed/16009870.

19. Osmond DH, Chin DP, Glassroth J, et al. Impact of bacterial pneumonia and Pneumocystis carinii pneumonia on human immunodeficiency virus disease progression. Pulmonary Complications of HIV Study Group. *Clin Infect Dis*. Sep 1999;29(3):536-543. Available at http://www.ncbi.nlm.nih.gov/pubmed/10530443.

20. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. Jul 1 2006;43(1):90-98. Available at http://www.ncbi.nlm.nih.gov/pubmed/16758423.

21. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Am J Respir Crit Care Med*. Dec 2000;162(6):2063-2068. Available at http://www.ncbi.nlm.nih.gov/pubmed/11112115.

22. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of Pneumocystis carinii pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. May 28 1998;12(8):885-893. Available at http://www.ncbi.nlm.nih.gov/pubmed/9631142.

23. Curran A, Falco V, Crespo M, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Med*. Oct 2008;9(8):609-615. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18557951.

24. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. Mar 1 2007;44 Suppl 2:S27-72. Available at http://www.ncbi.nlm.nih.gov/pubmed/17278083.

25. Jordano Q, Falco V, Almirante B, et al. Invasive pneumococcal disease in patients infected with HIV: still a threat in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Jun 1 2004;38(11):1623-1628. Available at http://www.ncbi.nlm.nih.gov/pubmed/15156452.

26. Hamel MJ, Greene C, Chiller T, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? *Am J Trop Med Hyg*. Sep 2008;79(3):320-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/18784222.

27. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of Pneumocystis carinii pneumonia, in the United States. *J Infect Dis*. May 1 2001;183(9):1409-1412. Available at http://www.ncbi.nlm.nih.gov/pubmed/11294675.

28. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *J Infect Dis*. Apr 1996;173(4):857-862. Available at

http://www.ncbi.nlm.nih.gov/pubmed/8603963.

29. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS*. Oct 1 1999;13(14):1971-1975. Available at http://www.ncbi.nlm.nih.gov/pubmed/10513657.
30. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med*. Sep 25 2000;160(17):2633-2638. Available at http://www.ncbi.nlm.nih.gov/pubmed/10999977.
31. Advisory Committee on Immunization P. Recommended adult immunization schedule: United States, October 2007-September 2008. *Ann Intern Med*. Nov 20 2007;147(10):725-729. Available at http://www.ncbi.nlm.nih.gov/pubmed/17947396.
32. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. *Vaccine*. May 7 2004;22(15-16):2006-2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/15121313.
33. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. Jun 17 2000;355(9221):2106-2111. Available at http://www.ncbi.nlm.nih.gov/pubmed/10902624.
34. Watera C, Nakiyingi J, Miiro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS*. May 21 2004;18(8):1210-1213. Available at http://www.ncbi.nlm.nih.gov/pubmed/15166540.
35. Centers for Disease C, Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. Oct 12 2012;61(40):816-819. Available at http://www.ncbi.nlm.nih.gov/pubmed/23051612.
36. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med*. Mar 4 2010;362(9):812-822. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20200385.
37. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis*. Oct 1 2007;45(7):e82-87. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17806042.
38. Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. *Clin Infect Dis*. Apr 1 2008;46(7):1093-1100. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18444830.
39. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998—2003. *Vaccine*. Oct 29 2008;26(46):5830-5834. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18786586.
40. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. Aug 6 2010;59(RR-8):1-62. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20689501.
41. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at http://www.ncbi.nlm.nih.gov/pubmed/10232311.
42. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. Dec 24 1992;327(26):1842-1848. Available at http://www.ncbi.nlm.nih.gov/pubmed/1448121.
43. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. Aug 8 1996;335(6):392-398. Available at http://www.ncbi.nlm.nih.gov/pubmed/8676932.

44. Oldfield EC, 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of Mycobacterium avium complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis*. Mar 1998;26(3):611-619. Available at http://www.ncbi.nlm.nih.gov/pubmed/9524832.

45. Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med*. 2005;20(12):1142-1145. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16423106&query_hl=100&itool=pubmed_docsum.

46. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis*. Jan 2000;181(1):158-164. Available at http://www.ncbi.nlm.nih.gov/pubmed/10608762.

47. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: A comparison of disease measurement strategies. *Medical care*. Aug 2006;44(8 Suppl 2):S52-60. Available at http://www.ncbi.nlm.nih.gov/pubmed/16849969.

48. Benard A, Mercie P, Alioum A, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS One*. 2010;5(1):e8896. Available at http://www.ncbi.nlm.nih.gov/pubmed/20126646.

49. Madeddu G, Laura Fiori M, Stella Mura M. Bacterial community-acquired pneumonia in HIV-infected patients. *Curr Opin Pulm Med*. May 2010;16(3):201-207. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20154625.

50. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. Jan 2010;14(1):e22-27. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19586789.

51. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus Streptococcus pneumoniae: coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis*. Jun 1 2009;48(11):1596-1600. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19400744.

52. Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. Aug 15 2004;170(4):440-444. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15184200.

53. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19440326.

54. Christensen D, Feldman C, Rossi P, et al. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clin Infect Dis*. 2005;41(4):554-556. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16028168&query_hl=88&itool=pubmed_docsum.

55. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *American journal of perinatology*. 1998;15(9):523-525. Available at http://www.ncbi.nlm.nih.gov/pubmed/9890248.

56. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiology and drug safety*. Dec 2000;9(7):549-556. Available at http://www.ncbi.nlm.nih.gov/pubmed/11338912.

57. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. Nov 1996;69(2):83-89. Available at http://www.ncbi.nlm.nih.gov/pubmed/8902438.

58. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. Jun 1998;42(6):1336-1339. Available at http://www.ncbi.nlm.nih.gov/pubmed/9624471.

59. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. May 2006;107(5):1120-1138. Available at http://www.ncbi.nlm.nih.gov/pubmed/16648419.

Bacterial Enteric Infections (Last updated May 3, 2016; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Rates of Gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population, but these rates decline when patients are on antiretroviral therapy (ART).[1-7] The risk of bacterial diarrhea varies according to CD4 T-lymphocyte (CD4) count and is greatest in individuals with clinical AIDS and/or <200 CD4 cells/mm^3.[5] The bacteria most frequently isolated by culture from HIV-infected adults in the United States are *Salmonella* (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter*. Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,[8] but their role is poorly understood because diagnosis remains a research-only test. *Clostridium difficile*-associated infection (CDI) is common in HIV-infected patients; recent data[9] suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to the traditional risk factors such as exposure to a health care facility or to antibiotics. Because community-onset CDI is increasingly recognized, health care providers should also consider CDI in the evaluation of outpatient diarrheal illnesses in HIV-infected individuals. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in HIV-infected individuals. Other enteric infections that may cause diarrhea, such as *Mycobacterium avium* complex (MAC) and cytomegalovirus, are discussed elsewhere in these guidelines.

As with bacterial enteric infections in HIV-uninfected persons, the probable source for most enteric infections in HIV-infected patients is ingestion of contaminated food or water.[3] Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*[10] and *Campylobacter*[11] (see Appendix for further details). HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase risk of enteric bacterial infections.

Clinical Manifestations

The three major clinical syndromes of infection with Gram-negative enteric bacteria among HIV-infected patients are:

- Self-limited gastroenteritis;
- More severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; and
- Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness.[12-15]

Severe community-associated diarrhea is often defined as ≥6 loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of disease such as fecal blood, orthostatic hypotension, or fever. In HIV-infected patients, the risk of more profound illness increases with the degree of immunosuppression.[1,3,4,16] Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in HIV-infected patients.[17-19]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (see below); a medication review, because diarrhea is a common side effect of some ART and antibiotics; quantification of the diarrheal illness by stool frequency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever. Physical examination should include measurement of temperature and assessment of volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood. Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in HIV-infected individuals, particularly those with advanced disease, blood cultures should be obtained from any patient with diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

Other infections for which HIV-infected patients are at risk, albeit at a lower rate, are non-jejuni non-coli Campylobacter species, such as *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari*, and the enterohepatic *Helicobacter* spp. (*Helicobacter cineadi* and *Helicobacter fennelliae*), which were originally described as *Campylobacter* spp. Blood culture systems will typically grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

A stool sample for *C. difficile* toxin or polymerase chain reaction (PCR) assay should be routinely performed for patients with diarrhea who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized), those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medications, and those with moderate-to-severe community-acquired diarrhea.[20] The most commonly used toxin tests are enzyme immunoassays that suffer from low sensitivity. PCR assays or glutamate dehydrogenase antigen enzyme immunoassays (which must be combined with a second confirmatory test for stool toxin) are recommended for testing.[21] However, only diarrheal stool samples should be tested for *C. difficile* to limit detection of asymptomatic colonization. Regardless of the test used, the diagnosis of CDI can only be made through careful selection of the correct population for testing and a correlation of clinical and laboratory findings.

Endoscopy should generally be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails. Endoscopy with biopsy may be required for diagnosing etiologies other than bacterial enteric infections, including cryptosporidiosis, microsporidiosis, cytomegalovirus or MAC gastroenteritis, and noninfectious causes of GI symptoms.

Clinicians should remain alert to the possibility of sexually transmitted disease (STD). Some sexually transmitted rectal infections (such as proctitis due to lymphogranuloma venereum or *Neisseria gonorrhoeae*) can produce symptoms similar to those seen with colitis due to *Salmonella*, *Shigella*, and *Campylobacter* spp. If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, diagnostic evaluation for STDs with anoscopy, culture, and biopsy should be considered.

Preventing Exposure

Multiple epidemiologic exposures can place patients at risk of enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures (detailed prevention recommendations related to food and water exposures, pet exposures, and travel-related exposures can be found in the Appendix). Providing advice and education about such exposures is the responsibility of the health care provider. A patient's clinical condition and CD4 count can help the provider determine what prevention recommendations are most appropriate. Patients with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[22] are at the greatest risk of enteric illnesses;[5] however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Patients should be advised to regularly wash their hands with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII)**. With regard to preventing enteric infection, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are only partially active against norovirus and *Cryptosporidium* **(AIII)**. HIV-infected patients should be advised to wash their hands

after potential contact with human feces, such as through defecation, cleaning feces from infants, or contact with a person who has diarrhea; after handling pets or other animals; after gardening or other contact with soil; before preparing food and eating; and before and after sex **(AIII)**. HIV-infected patients should avoid unprotected sex practices, such as anal sex and oral-anal contact that could result in oral exposure to feces and, in addition to handwashing, they should be advised to use barriers such as dental dams during sex to reduce exposures when possible **(AIII)**.

Preventing Disease

Antimicrobial prophylaxis to prevent bacterial enteric illness is usually **not recommended**, including for travelers **(AIII)**. Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase risk of CDI. In rare cases, however, antimicrobial prophylaxis with fluoroquinolones or rifaximin can be considered, such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII)**. For pregnant women and patients already taking trimethoprim-sulfamethoxazole (TMP-SMX) (such as for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolones or rifaximin **(BIII)**. Risk of toxicity should be considered before prophylaxis with TMP-SMX is initiated solely because of travel.

Treating Disease

Empiric Therapy

In most situations, treatment of diarrheal disease in HIV-infected patients does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status. Patients should be informed of the importance of maintaining hydration and be given oral or intravenous (IV) rehydration, if indicated **(AIII)**. Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates also are likely to be useful **(BIII)**. The effectiveness and safety of probiotics or antimotility agents have not been adequately studied in HIV-infected patients with diarrheal illnesses.[23] Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI **(BIII)**.

After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depend upon the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. No further work-up may be necessary and no treatment other than oral rehydration required, for example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood. However, a short course of antibiotics may be indicated in HIV-infected patients with CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with advanced HIV disease, that is, CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness, with clinically severe diarrhea (i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. Empiric therapy with ciprofloxacin is reasonable **(AIII)**. IV ceftriaxone or IV cefotaxime are reasonable alternatives **(BIII)**. Therapy should be adjusted subsequently based on the results of the diagnostic work-up. Diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity, such as bloody stool or dehydration, should be evaluated and directed therapy should be started once a diagnosis is confirmed.

Diarrhea is one of the most common illnesses affecting international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is an important public health problem. For example, traveler's diarrhea caused by fluoroquinolone resistant *Campylobacter jejuni* in Southeast Asia is common.[24] Clinicians should consider the possibility of a resistant infection when prescribing empiric therapy for HIV-infected travelers who experience diarrhea or a syndrome consistent with a systemic

infection while traveling or upon returning to the United States, given reports of multidrug resistant *Enterobacteriaceae* acquisition during travel.[25-29]

Pathogen-Specific Therapy

Salmonella spp.

Immunocompetent hosts who are not HIV-infected often do not require treatment for *Salmonella* gastroenteritis, as the condition is usually self-limited and treatment may prolong the carrier state. In contrast, all HIV-infected patients with salmonellosis should be treated **(AIII)**, although no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20- to 100-fold and mortality as much as 7-fold compared with that in patients who are not HIV-infected.[1,30]

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone **(AIII)**. Ciprofloxacin is the preferred agent **(AIII)**.[31] Other fluoroquinolones, such as levofloxacin and moxifloxacin, would likely be effective in treating salmonellosis in HIV-infected patients but they have not been well evaluated in clinical studies **(BIII)**. Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins such as ceftriaxone or cefotaxime **(BIII)**.

The optimal duration of therapy for HIV-related *Salmonella* infection has not been defined. For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable. For the same patients with bacteremia, 14 days is appropriate, provided clearance of bacteremia is documented. Longer treatment is suggested if bacteremia persists or if the infection is complicated, that is, if metastatic foci are present **(BIII)**. For patients with advanced HIV disease (CD4 count <200 cells/mm^3), 2 to 6 weeks of antibiotics is often recommended **(CIII)**.[32] Some patients with Salmonella bacteremia may remain febrile for 5 to 7 days despite effective therapy.

HIV-infected patients with *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment **(BIII)**. Recurrence may present as bacteremia or as an anatomically localized infection, including intra-abdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci. Secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and it might also be considered for patients with recurrent gastroenteritis (with or without bacteremia) and in those with CD4 counts <200 cell/mm^3 with severe diarrhea **(BIII)**. The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness[33] and suppression of HIV replication with ART appears to decrease the risk of recurrent illnesses.[34] In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis can probably be stopped **(CII)**.[7] Clinicians also should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Shigella spp.

Therapy for *Shigella* infections is recommended both to shorten the duration of illness and to possibly prevent spread of the infection to others **(AIII)**.[31] The recommended treatment for shigellosis is with a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days **(AIII)**. However, ciprofloxacin-resistant *S. sonnei* has been reported in the United States and is associated with international travel, homelessness, and being a man who has sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[29] Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) **(BIII)**. Azithromycin has not been evaluated in HIV-infected patients with shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[35] Recently, azithromycin-resistant *Shigella* spp in HIV-infected MSM have been reported.[36-38] Treatment for patients with *Shigella* bacteremia is less well defined, but

extending treatment to at least 14 days is reasonable **(BIII)**. Azithromycin **is not recommended** for treatment of *Shigella* spp. bacteremia **(AIII)**. Chronic suppressive or maintenance therapy **is not recommended** for first-time *Shigella* infections **(BIII)**. Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm^3, in which case extending antimicrobial therapy for up to 6 weeks is reasonable **(BIII)**. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter spp.

The optimal treatment of campylobacteriosis in HIV-infected patients is poorly defined. Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII)**. Rates of resistance to antimicrobial agents differs by *Campylobacter* species. In the United States in 2013, 22% of *C. jejuni* isolates were resistant to fluoroquinolone and 2% were resistant to azithromycin; among *C. coli* isolates, 35% of isolates were resistant to fluoroquinolones and 17% were resistant to azithromycin.[24] For patients with mild disease and CD4 counts >200 cells/mm^3, some clinicians opt to withhold therapy unless symptoms persist for more than several days **(CIII)**. For mild-to-moderate campylobacteriosis, initiating therapy with a fluoroquinolone such as ciprofloxacin for 7 to 10 days (if the organism is sensitive) or azithromycin for 5 days is a reasonable approach **(BIII)**. Azithromycin has not been evaluated in HIV-infected patients with campylobacteriosis and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[39] Patients with *Campylobacter* bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive **(BIII)**. Azithromycin is **not recommended** for treatment of *Campylobacter* bacteremia **(AIII)**. Adding a second active agent, such as an aminoglycoside, may be prudent in these patients to limit the emergence of antibiotic resistance **(BIII)**. Antibiotic choice should be guided by antibiotic susceptibility tests. Chronic suppressive or maintenance therapy is **not recommended** for first-time *Campylobacter* infections in HIV-infected patients **(BIII)**. However, recurrent infections can occur, particularly in patients with CD4 counts <200 cells/mm^3. In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII)**. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.

Clostridium difficile

Available data suggest that HIV-infected patients respond to treatment of CDI similarly to HIV-uninfected patients. Guidelines and subsequent updates to guide the treatment of CDI have been published[40-43] and can be consulted for further information. Multivariate analysis of two recent identical, multicenter (91 sites in United States, Canada; 109 sites in Europe), randomized, double-blind studies involving 537 non-HIV-infected patients with CDI (278 and 259 treated with metronidazole and vancomycin, respectively) found vancomycin to be superior to metronidazole for clinical success [OR 1.575 (1.035,2.396), $P = 0.034$]. Stratification by CDI disease severity found 4.0% (mild), 8.3% (moderate), and 12.2% (severe) improved clinical success rates with vancomycin therapy.[44] Given this trial and earlier data,[45] vancomycin **(AI)** is recommended for treatment of HIV-infected persons with CDI with the possible exception of mild CDI where treatment with metronidazole **(CII)** may yield clinical success. Treatment of recurrent CDI in HIV-infected patients is the same as in patients who are not HIV-infected. Limited case reports suggest that fecal microbiota therapy may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**.[46] The impact of ART on recurrence of CDI is unknown.

Special Considerations with Regard to Starting ART

ART initiation should follow standard guidelines. The presence of a diarrheal illness is relevant only in terms of a patient's ability to ingest and absorb ART. If recurrent enteric infections are documented and/or *Salmonella* bacteremia occurs, prompt initiation of ART should be considered regardless of CD4 count; in other words, the presence of an enteric infection should not delay ART initiation **(BIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored closely for response to treatment, defined clinically by improvement in systemic signs and symptoms, resolution of diarrhea, and sterilization of infected tissues or body fluids such as blood. A follow-up stool culture to demonstrate clearance of the organism is not required if clinical symptoms and diarrhea resolve. Follow-up stool culture may be required when public health considerations and state law dictate the need to ensure micro¬biologic cure, such as in health care or food service workers.

Immune reconstitution inflammatory syndrome has not been described in association with treatment for bacterial enteric pathogens.

Managing Treatment Failure

Follow-up stool culture should be considered for patients who fail to respond clinically to appropriate antimicrobial therapy. In patients with persistent or recurrent diarrhea despite therapy, clinicians should consider other enteric infections in the context of the patient's immune status and, in all cases, the possibility of C. difficile or the development of antimicrobial resistance.

Observational studies suggest that plasma drug concentrations (e.g., of ciprofloxacin) in HIV-infected patients may be decreased as a result of diarrhea or malabsorption.[47,48] Coadministration of quinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these interfere with drug absorption. Although larger prospective studies are needed to determine the impact of severe diarrhea on antibiotic absorption, it is prudent to use IV antibiotics in clinically unstable patients **(AIII)**.

Preventing Recurrence

The pharmacologic approach to recurrent enteric infections is covered in the section on directed therapy for each bacterial species. As noted above, secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and, in some circumstances, for those with recurrent shigellosis **(BIII)** or campylobacteriosis **(BIII)**.

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infection in pregnant women is the same as in women who are not pregnant. Bacterial enteric infections in pregnant women should be managed the same as in women who are not pregnant, with several considerations. Based on the safety profile, expanded-spectrum cephalosporins or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing **(BIII)**.[49] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[50-52] Thus, quinolones can be used in pregnancy for bacterial enteric infections in HIV-infected pregnant women if indicated by susceptibility testing or failure of first-line therapy, as listed above **(BIII)**. TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII)**.[53,54,55] However, a recent review of potential risks related to TMP-SMX use cites the low quality of current data and supports use of TMP-SMX in HIV-infected pregnant women as clinically indicated.[56] Neonatal care providers should be informed if maternal sulfa therapy was used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus in the newborn. Since rifaximin is not systemically absorbed, it can be used in pregnancy as in non-pregnant individuals.

Recommendations for Preventing and Treating Bacterial Enteric Infections (page 1 of 3)

Preventing Bacterial Enteric Illness

- Antimicrobial prophylaxis to prevent bacterial enteric illness usually **is not recommended**, including for travelers **(AIII)**.
- In rare cases, such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration, antimicrobial prophylaxis with fluoroquinolones or rifaximin can be considered **(CIII)**.
- For pregnant women and patients already on trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis against *Pneuomcystis jirovecii*, TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolone or rifaximin **(BIII)**.

General Considerations when Managing Patients with Bacterial Enteric Infections

- Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea **(AIII)**.
- Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium difficile* infection (CDI) **(BIII)**.
- Diagnostic fecal specimens should be obtained prior to initiation of empiric antimicrobial therapy.
- If stool sample is obtained, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance.
- Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/mm^3. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response after 3 to 4 days, consider follow-up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug-drug interactions.
- Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Empiric Treatment of Bacterial Enteric Infections (Pending Diagnostic Studies)

For patients with advanced HIV (CD4 count <200 cells/mm^3 or concomitant AIDS-defining illnesses) and clinically severe diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills).

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy:

- Ceftriaxone IV 1 g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

Note: IV antibiotic therapy with hospitalization should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease.

For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed.

Diarrhea is a common illness of international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is common. Clinicians should consider the possibility of resistant infections when prescribing empiric antibiotic therapy for HIV-infected travelers while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia.

Treating Salmonellosis

All HIV-infected patients with salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20-100 fold) and mortality (by as much as 7-fold) compared to HIV-negative individuals **(AIII)**.

Preferred Therapy for Salmonella Gastroenteritis With or Without Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy:

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**, *or*

If susceptible, alternatives to fluroquinolone may include one of the following:

- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) q12h **(BIII)**, *or*
- Ceftriaxone IV 1g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count >200 cells/mm^3: 7–14 days **(BIII)**
- If CD4 count <200 cells/mm^3 particularly if primary illness was severe: 2–6 weeks **(BIII)**

Duration of Therapy for Gastroenteritis with Bacteremia

- If CD4 count >200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present) **(BIII)**
- If CD4 count <200 cells/mm^3: 2–6 weeks **(BIII)**

Secondary Prophylaxis

- The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure **(BIII)**. Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.
- Suppression of HIV replication with ART is expected to decrease the risk of recurrent illnesses.
- Clinicians should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Some Experts Recommend Secondary Prophylaxis For:

- Patients with recurrent bacteremia or
- Patients with recurrent gasteroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 and severe diarrhea **(CIII)**

When To Stop Secondary Prophylaxis:

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3 **(CII)**

Treating Shigellosis

Therapy is indicated to shorten the duration of illness and to possibly prevent spread to others **(AIII)**. However, given increasing antimicrobial resistance and limited data demonstrating that antibiotic therapy limits transmission, antibiotic treatment may be withheld in HIV-infected patients with CD4 >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection **(CIII)**.

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin (PO or IV) 400 mg q24h **(BIII)**
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV q12h **(BIII)**
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: azithromycin **is not recommended** for *Shigella* bacteremia **[AIII]**)

Duration of Therapy:

- Gastroenteritis: 7–10 days **(AIII)** (except azithromycin, treat for 5 days)
- Bacteremia: ≥14 days **(BIII)**
- Recurrent Infections: up to 6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy:

- Not recommended for first-time *Shigella* infections **(BIII)**

Recommendations for Preventing and Treating Bacterial Enteric Infections (page 3 of 3)

Treating Campylobacteriosis

- Optimal treatment is poorly defined.
- There is an increasing rate of fluoroquinolone resistance in the United States (22% resistance in 2013 among *C. jejuni* isolates).
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild disease if CD4 count >500 cells/mm^3:

- If diarrhea resolves prior to culture confirmation of *Campylobacter* infection, antibiotic treatment can be withheld **(CIII)**. If symptoms persist, consider antibiotic therapy **(CIII)**.

Mild to Moderate Disease:

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)**—if susceptible, or
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (**Not recommended** for bacteremia **[AIII]**)

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg PO or IV q24h **(BIII)**, *or*
- Moxifloxacin 400 mg PO or IV q24h **(BIII)**

Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)** + an aminoglycoside **(BIII)** in bacteremic patients to limit the emergence of antibiotic resistance

Duration of Therapy:

- Gastroenteritis: 7–10 days **(BIII)** [5 days if azithromycin is used]
- Bacteremia: ≥14 days **(BIII)**
- Recurrent bacteremic disease: 2–6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy:

- Not recommended for first-time *Campylobacter* infections **(BIII)**

Treating *Clostridium difficile* Infection (CDI)

Preferred Therapy

- Vancomycin 125 mg (po) four times per day X 10-14 days **(AI)**
- For severe, life-threatening CDI, see text and references for additional information.

Alternative Therapy for Mild CDI

- For mild, outpatient disease: metronidazole 500 mg (po) three times per day **(CII)**

Recurrent CDI

- Treatment is the same as in patients without HIV infection. Fecal microbiota therapy (FMT) may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**. See text and references for additional information.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; IV = intravenously; PO = orally; q(n)h = every "n" hours.

References

1. Celum CL, Chaisson RE, Rutherford GW, Barnhart JL, Echenberg DF. Incidence of salmonellosis in patients with AIDS. *J Infect Dis*. Dec 1987;156(6):998-1002. Available at http://www.ncbi.nlm.nih.gov/pubmed/3680999.
2. Sorvillo FJ, Lieb LE, Waterman SH. Incidence of campylobacteriosis among patients with AIDS in Los Angeles County. *J Acquir Immune Defic Syndr*. 1991;4(6):598-602. Available at http://www.ncbi.nlm.nih.gov/pubmed/2023099.
3. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. *Clin Infect Dis*. Aug 1995;21 Suppl 1:S84-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/8547518.
4. Nelson MR, Shanson DC, Hawkins DA, Gazzard BG. Salmonella, Campylobacter and Shigella in HIV-seropositive patients. *AIDS*. Dec 1992;6(12):1495-1498. Available at http://www.ncbi.nlm.nih.gov/pubmed/1362879.
5. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002.

Clin Infect Dis. Dec 1 2005;41(11):1621-1627. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267735.

6. Wilcox CM, Saag MS. Gastrointestinal complications of HIV infection: changing priorities in the HAART era. *Gut*. Jun 2008;57(6):861-870. Available at http://www.ncbi.nlm.nih.gov/pubmed/18203808.
7. Hung CC, Hung MN, Hsueh PR, et al. Risk of recurrent nontyphoid Salmonella bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. *Clin Infect Dis*. Sep 1 2007;45(5):e60-67. Available at http://www.ncbi.nlm.nih.gov/pubmed/17682981.
8. Huang DB, Mohanty A, DuPont HL, Okhuysen PC, Chiang T. A review of an emerging enteric pathogen: enteroaggregative Escherichia coli. *J Med Microbiol*. Oct 2006;55(Pt 10):1303-1311. Available at http://www.ncbi.nlm.nih.gov/pubmed/17005776.
9. Haines CF, Moore RD, Bartlett JG, et al. Clostridium difficile in a HIV-infected cohort: incidence, risk factors, and clinical outcomes. *AIDS*. Nov 13 2013;27(17):2799-2807. Available at http://www.ncbi.nlm.nih.gov/pubmed/23842125.
10. Aragon TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. *Clin Infect Dis*. Feb 1 2007;44(3):327-334. Available at http://www.ncbi.nlm.nih.gov/pubmed/17205436.
11. Quinn TC, Goodell SE, Fennell C, et al. Infections with Campylobacter jejuni and Campylobacter-like organisms in homosexual men. *Ann Intern Med*. Aug 1984;101(2):187-192. Available at http://www.ncbi.nlm.nih.gov/pubmed/6547580.
12. Snijders F, Kuijper EJ, de Wever B, van der Hoek L, Danner SA, Dankert J. Prevalence of Campylobacter-associated diarrhea among patients infected with human immunodeficiency virus. *Clin Infect Dis*. Jun 1997;24(6):1107-1113. Available at http://www.ncbi.nlm.nih.gov/pubmed/9195065.
13. Tee W, Mijch A. Campylobacter jejuni bacteremia in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients: comparison of clinical features and review. *Clin Infect Dis*. Jan 1998;26(1):91-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/9455515.
14. Tee W, Mijch A, Wright E, Yung A. Emergence of multidrug resistance in Campylobacter jejuni isolates from three patients infected with human immunodeficiency virus. *Clin Infect Dis*. Sep 1995;21(3):634-638. Available at http://www.ncbi.nlm.nih.gov/pubmed/8527556.
15. Meier PA, Dooley DP, Jorgensen JH, Sanders CC, Huang WM, Patterson JE. Development of quinolone-resistant Campylobacter fetus bacteremia in human immunodeficiency virus-infected patients. *J Infect Dis*. Apr 1998;177(4):951-954. Available at http://www.ncbi.nlm.nih.gov/pubmed/9534967.
16. Casado JL, Valdezate S, Calderon C, et al. Zidovudine therapy protects against Salmonella bacteremia recurrence in human immunodeficiency virus-infected patients. *J Infect Dis*. Jun 1999;179(6):1553-1556. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10228081.
17. Kristjansson M, Viner B, Maslow JN. Polymicrobial and recurrent bacteremia with Shigella in a patient with AIDS. *Scand J Infect Dis*. 1994;26(4):411-416. Available at http://www.ncbi.nlm.nih.gov/pubmed/7984973.
18. Mayer KH, Hanson E. Recurrent salmonella infection with a single strain in the acquired immunodeficiency syndrome. Confirmation by plasmid fingerprinting. *Diagn Microbiol Infect Dis*. Jan 1986;4(1):71-76. Available at http://www.ncbi.nlm.nih.gov/pubmed/3510806.
19. Rubino S, Spanu L, Mannazzu M, et al. Molecular typing of non-typhoid Salmonella strains isolated from HIV-infected patients with recurrent salmonellosis. *AIDS*. Jan 14 1999;13(1):137-139. Available at http://www.ncbi.nlm.nih.gov/pubmed/10207558.
20. Pulvirenti JJ, Mehra T, Hafiz I, et al. Epidemiology and outcome of Clostridium difficile infection and diarrhea in HIV infected inpatients. *Diagn Microbiol Infect Dis*. Dec 2002;44(4):325-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/12543536.
21. Brecher SM, Novak-Weekley SM, Nagy E. Laboratory diagnosis of Clostridium difficile infections: there is light at the end of the colon. *Clin Infect Dis*. Oct 2013;57(8):1175-1181. Available at http://www.ncbi.nlm.nih.gov/pubmed/23788237.
22. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep*. Dec 5 2008;57(RR-10):1-12. Available at http://www.ncbi.nlm.nih.gov/pubmed/19052530.

23. Nwachukwu CE, Okebe JU. Antimotility agents for chronic diarrhoea in people with HIV/AIDS. *Cochrane Database Syst Rev*. 2008(4):CD005644. Available at http://www.ncbi.nlm.nih.gov/pubmed/18843696.

24. Centers for Disease Control and Prevention. 2013 Human Isolates Final Report. 2015. Available at http://www.cdc.gov/narms/pdf/2013-annual-report-narms-508c.pdf.

25. Lubbert C, Straube L, Stein C, et al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol*. Jan 2015;305(1):148-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/25547265.

26. Kantele A, Laaveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. *Clin Infect Dis*. Mar 15 2015;60(6):837-846. Available at http://www.ncbi.nlm.nih.gov/pubmed/25613287.

27. Johnning A, Kristiansson E, Angelin M, et al. Quinolone resistance mutations in the faecal microbiota of Swedish travellers to India. *BMC Microbiol*. 2015;15:235. Available at http://www.ncbi.nlm.nih.gov/pubmed/26498929.

28. Barlow RS, Debess EE, Winthrop KL, Lapidus JA, Vega R, Cieslak PR. Travel-associated antimicrobial drug-resistant nontyphoidal Salmonellae, 2004-2009. *Emerg Infect Dis*. Apr 2014;20(4):603-611. Available at http://www.ncbi.nlm.nih.gov/pubmed/24655581.

29. Centers for Disease Control and Prevention. Importation and Domestic Transmission of Shigella sonnei Resistant to Ciprofloxacin — United States, May 2014–February 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(12):318-320. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6412a2.htm?s_cid=mm6412a2_w.

30. Cummings PL, Sorvillo F, Kuo T. Salmonellosis-related mortality in the United States, 1990-2006. *Foodborne Pathog Dis*. Nov 2010;7(11):1393-1399. Available at http://www.ncbi.nlm.nih.gov/pubmed/20617938.

31. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. Feb 1 2001;32(3):331-351. Available at http://www.ncbi.nlm.nih.gov/pubmed/11170940.

32. Gordon MA, Banda HT, Gondwe M, et al. Non-typhoidal salmonella bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. *AIDS*. Aug 16 2002;16(12):1633-1641. Available at http://www.ncbi.nlm.nih.gov/pubmed/12172085.

33. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. Dec 18 1992;41(RR-17):1-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/1361652.

34. Chou YJ, Lin HW, Yang CJ, et al. Risk of recurrent nontyphoid Salmonella bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy. *J Microbiol Immunol Infect*. Jul 31 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26316009.

35. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. A double-blind, randomized, controlled trial. *Ann Intern Med*. May 1 1997;126(9):697-703. Available at http://www.ncbi.nlm.nih.gov/pubmed/9139555.

36. Heiman KE, Karlsson M, Grass J, et al. Notes from the field: Shigella with decreased susceptibility to azithromycin among men who have sex with men - United States, 2002-2013. *MMWR Morb Mortal Wkly Rep*. Feb 14 2014;63(6):132-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/24522098.

37. Hassing RJ, Melles DC, Goessens WH, Rijnders BJ. Case of Shigella flexneri infection with treatment failure due to azithromycin resistance in an HIV-positive patient. *Infection*. Feb 2 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24488332.

38. Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. *Lancet Infect Dis*. Aug 2015;15(8):913-921. Available at http://www.ncbi.nlm.nih.gov/pubmed/25936611.

39. Kuschner RA, Trofa AF, Thomas RJ, et al. Use of azithromycin for the treatment of Campylobacter enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis*. Sep 1995;21(3):536-541. Available at http://www.ncbi.nlm.nih.gov/pubmed/8527539.

40. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. May 2010;31(5):431-455. Available at http://www.ncbi.nlm.nih.gov/pubmed/20307191.

41. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. Apr 2013;108(4):478-498; quiz 499. Available at http://www.ncbi.nlm.nih.gov/pubmed/23439232.

42. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. *JAMA*. Jan 27 2015;313(4):398-408. Available at http://www.ncbi.nlm.nih.gov/pubmed/25626036.

43. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med*. Apr 16 2015;372(16):1539-1548. Available at http://www.ncbi.nlm.nih.gov/pubmed/25875259.

44. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. Aug 2014;59(3):345-354. Available at http://www.ncbi.nlm.nih.gov/pubmed/24799326.

45. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. Aug 1 2007;45(3):302-307. Available at http://www.ncbi.nlm.nih.gov/pubmed/17599306.

46. Di Bella S, Gouliouris T, Petrosillo N. Fecal microbiota transplantation (FMT) for Clostridium difficile infection: Focus on immunocompromised patients. *J Infect Chemother*. Apr 2015;21(4):230-237. Available at http://www.ncbi.nlm.nih.gov/pubmed/25703532.

47. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis*. Jan 15 2004;38(2):280-283. Available at http://www.ncbi.nlm.nih.gov/pubmed/14699462.

48. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications. *N Engl J Med*. Oct 7 1993;329(15):1122-1123. Available at http://www.ncbi.nlm.nih.gov/pubmed/8371737.

49. Bérard A, Sheehy O, Zhao J, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiology and Drug Safety*. 2015;24(12):1241-1248. Available at

50. Padberg S, Wacker E, Meister R, et al. Observational cohort study of pregnancy outcome after first-trimester exposure to fluoroquinolones. *Antimicrob Agents Chemother*. Aug 2014;58(8):4392-4398. Available at http://www.ncbi.nlm.nih.gov/pubmed/24841264.

51. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. Nov 1996;69(2):83-89. Available at http://www.ncbi.nlm.nih.gov/pubmed/8902438.

52. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. Jun 1998;42(6):1336-1339. Available at http://www.ncbi.nlm.nih.gov/pubmed/9624471.

53. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at http://www.ncbi.nlm.nih.gov/pubmed/11738517.

54. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at http://www.ncbi.nlm.nih.gov/pubmed/11096168.

55. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. May 15 2001;153(10):961-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/11384952.

56. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. Aug 15 2014;66(5):512-521. Available at http://www.ncbi.nlm.nih.gov/pubmed/24853309.

Bartonellosis (Last updated May 7, 2013; last reviewed March 13, 2017)

Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur only in individuals who are immunocompromised. BA is caused by either *Bartonella quintana* or *Bartonella henselae*.[1,2] Twenty-four species and three subspecies of *Bartonella* have been isolated and are officially recognized (http://www.bacterio.cict.fr/b/bartonella.html), and eight have been isolated from humans. However, only *B. henselae* and *B. quintana* infections have been identified in HIV-infected patients.[2] BA most often occurs late in HIV infection, in patients with median CD4 T lymphocyte (CD4 cell) counts <50 cells/mm^3.[2] In HIV-infected patients, bartonellosis is often a chronic illness, lasting for months to years, with BA lesions and intermittent bacteremia.

Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients with HIV infection.[2] In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.[2] The body louse serves as the vector of *B. quintana* in humans. To avoid exposure to *B. quintana*, HIV-infected patients should avoid body lice and, if infected, treat the infestation. The cat flea is the vector of *B. henselae* in cats. Cats are the most common vector (via a scratch) responsible for transmitting *B. henselae* to humans, most likely when their claws become contaminated with feces from *B. henselae*-infected fleas. In some areas of the United States, the prevalence of *B. henselae* bacteremia in pet cats approaches 50%.[3] Control of cat flea infestation and avoidance of cat scratches are therefore critical strategies for preventing *B. henselae* infections in patients who are HIV infected.

Clinical Manifestations

BA lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. These lesions can be clinically indistinguishable from Kaposi sarcoma, pyogenic granuloma, and other skin conditions. BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* can cause bacillary peliosis hepatis. Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in patients with late-stage AIDS and should be considered in the differential diagnosis of patients with fever and CD4 counts <100 cells/mm^3.[4] *Bartonella* is a relatively common cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana* and, less frequently, *B. henselae*.[5]

Diagnosis

Diagnosis can be confirmed by histopathologic examination of biopsied tissue.[6] BA lesions are characterized by vascular proliferation, and a modified silver stain (such as Warthin-Starry stain) usually demonstrates numerous bacilli. Tissue Gram staining and acid-fast staining are negative.

A well-characterized serologic test was developed at Centers for Disease Control and Prevention[7] and is also available at some state health labs. In addition, several private laboratories offer serological testing, but none of these private laboratory tests has been evaluated for sensitivity or specificity with sera from HIV-infected patients with culture-documented *Bartonella* infection. In immunocompetent patients, anti-*Bartonella* antibodies might not be detectable for 6 weeks after acute infection; in contrast, by the time *Bartonella* infection is suspected in patients with late-stage HIV infection, they usually have been infected for months or even >1 year. Note that as many as 25% of *Bartonella* culture-positive patients never develop antibodies in the setting of advanced HIV infection.[4] In those patients who do develop anti-*Bartonella* antibodies, monitoring of antibody levels can correlate with resolution and recrudescence of *Bartonella* infection.

Bartonella species can be isolated (with difficulty) from blood, using ethylenediaminetetraacetic acid (EDTA) tubes. The organisms have been isolated from tissue in only a few laboratories because of the fastidious nature of *Bartonella*.[2] Polymerase chain reaction methods have been developed for identification and speciation of *Bartonella* but are not widely available.

Preventing Exposure

HIV-infected patients, specifically those who are severely immunocompromised (CD4 counts <100 cells/mm^3), are at high risk of severe disease when infected by *B. quintana* and *B. henselae*. The major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised individuals should consider the potential risks of cat ownership **(AIII)**. Patients who want cats should acquire animals that are older than age 1 year and in good health **(BII)**. Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but HIV-infected individuals should avoid rough play with cats and situations in which scratches are likely **(AII)**. Patients should avoid contact with flea feces (i.e., flea dirt), and any cat-associated wound should be washed promptly with soap and water **(BIII)**. Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian **(BIII)**. No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats **(BII)**. The major risk factor for *B. quintana* infection is body lice infestation. Patients who are homeless or in marginal housing should be informed that body louse infestation can be associated with serious illness and provided with appropriate measures to eradicate body lice, if present **(AII)**.

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended **(BIII)**. However, note that in a retrospective case-control study, *Mycobacterium avium* complex prophylaxis using a macrolide or rifamycin was protective against developing *Bartonella* infection.[2]

Treating Disease

All HIV-infected patients with *Bartonella* infection should receive antibiotic treatment **(AII)**. Guidelines for treatment of *Bartonella* infections have been published.[8] No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in HIV-infected patients. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII)**.[1,2] Therapy should be administered for ≥3 months **(AII)**. Doxycycline, with or without a rifamycin, is the treatment of choice for bartonellosis infection involving the central nervous system (CNS) **(AIII)**. For severe *Bartonella* infections, combination therapy using erythromycin or doxycycline with a rifamycin is recommended **(BIII)**; intravenous therapy may be needed initially **(AIII)**. Treatment of confirmed *Bartonella* endocarditis should include doxycycline with the addition of gentamicin for 2 weeks (if tolerated); a rifamycin can be substituted for gentamicin in the setting of renal insufficiency **(BII)**.[8]

Clarithromycin or azithromycin treatment has been associated with clinical response and either of these can be an alternative therapy *Bartonella* infections (except for endocarditis or CNS infections) **(BIII)**. Azithromycin is recommended for patients who are less likely to comply with the more frequent dosing schedule for doxycycline or erythromycin. A third-generation cephalosporin, ceftizoxime,[9] was used successfully to treat *Bartonella* in a pregnant HIV-infected woman, but because there are no other data, a macrolide is the drug of first choice. Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(BII)**. Quinolones and trimethoprim-sulfamethoxazole (TMP-SMX) have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(BIII)**.

Special Consideration with Regard to Starting ART

Antiretroviral-naive patients with *Bartonella* CNS or ophthalmic lesions should probably be treated with doxycycline and a rifamycin for 2 to 4 weeks before instituting antiretroviral therapy **(CIII)**.

Monitoring of Response to Therapy and Adverse Effects (Including IRIS)

Patients should have anti-*Bartonella* IgG antibody titers checked at the time of diagnosis and, if positive, should be followed with sequential titers every 6 to 8 weeks until a four-fold decrease is documented. This test is available at the Centers for Disease Control and Prevention and several large commercial labs. Patients treated with oral doxycycline should be cautioned about pill-associated ulcerative esophagitis that occurs most often when a dose is taken with only a small amount of liquid or at night just before retiring.[10] Photosensitivity also can occur during doxycycline treatment. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels. Serious side effects can occur during treatment with rifamycins, including hypersensitivity reactions (including thrombocytopenia, interstitial nephritis, and hemolytic anemia), and hepatitis. Administration of rifamycins strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many ARV drugs, are taken simultaneously.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with Bartonellosis and treatment with ART in HIV-infected persons.

Managing Treatment Failure

Among patients who fail to respond to initial treatment, 1 or more of the second-line alternative regimens should be considered **(AIII)**, again with treatment duration of ≥3 months. For patients with positive or increasing antibody titers, treatment should continue until a fourfold decrease is documented.

Preventing Recurrence

If a relapse occurs after a minimum 3-month course of primary treatment, long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the CD4 count remains <200 cells/mm^3 **(AIII)**.

Long-term suppression can be discontinued after the patient has received at least 3 to 4 months of therapy and when the CD4 count remains >200 cells/mm^3 for ≥6 months **(CIII)**. Some specialists would discontinue therapy only if the *Bartonella* titers have also decreased by four-fold **(CIII)**.

Special Considerations During Pregnancy

Infection with *Bartonella bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death.[11] No data are available on the effect of *B. henselae* or *B. quintana* infections in pregnant women with concomitant HIV infection.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in non-pregnant women. Erythromycin treatment should be used **(AIII)** rather than tetracyclines during pregnancy because of the increased risk of hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins such as ceftizoxime[9] or ceftriaxone may have efficacy against *Bartonella* in pregnant women who are HIV infected, but it should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins **are not recommended** because of their lack of efficacy against *Bartonella* **(AII)**.

Recommendations for Treating *Bartonella* Infections

Preferred Therapy

For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis:

- Doxycycline 100 mg PO or IV q12h **(AII)**, *or*
- Erythromycin 500 mg PO or IV q6h **(AII)**

For Infections Involving the CNS:

- Doxycycline 100 mg PO or IV q12h +/- rifampin 300 mg PO or IV q12h **(AIII)**

For Confirmed Bartonella Endocarditis:

- (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**, *or*
- For patients with renal insufficiency: (doxycycline 100 mg IV q12h + rifampin 300 mg IV or PO q12h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**

For Other Severe Infections

- Doxycycline 100 mg PO or IV q12h + rifampin 300 mg PO or IV q12h **(BIII)**, *or*
- Erythromycin 500 mg PO or IV q6h + rifampin 300 mg PO or IV q12h **(BIII)**

Alternative Therapy for Bartonella Infections (Not for Endocarditis or CNS Infections):

- Azithromycin 500 mg PO daily **(BIII)**, *or*
- Clarithromycin 500 mg PO BID **(BIII)**

Duration of Therapy:

- At least 3 months

Indication for Long-Term Suppressive Therapy

If a relapse occurs after a ≥3 month course of primary treatment:

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm^3 **(AIII)**

*Indications for Discontinuing Long-Term Suppressive Therapy **(CIII)**:*

- Received at least 3 to 4 months of treatment; and
- CD4 count >200 cells/mm^3 for at least 6 months
- Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by four-fold

Other Considerations

- Rifampin is a potent hepatic enzyme inducer and may lead to significant interaction with many drugs; including ARV agents (see Table 5 for dosing recommendations)

Key to Abbreviations: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, IV = intravenously, PO = orally; q(n)h = every "n" hours

References

1. Spach DH, Koehler JE. Bartonella-associated infections. *Infect Dis Clin North Am*. Mar 1998;12(1):137-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/9494835.
2. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. *N Engl J Med*. Dec 25 1997;337(26):1876-1883. Available at http://www.ncbi.nlm.nih.gov/pubmed/9407154.
3. Koehler JE, Glaser CA, Tappero JW. Rochalimaea henselae infection. A new zoonosis with the domestic cat as reservoir. *JAMA*. Feb 16 1994;271(7):531-535. Available at http://www.ncbi.nlm.nih.gov/pubmed/8301768.
4. Koehler JE, Sanchez MA, Tye S, et al. Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis*. Aug 15 2003;37(4):559-566. Available at http://www.ncbi.nlm.nih.gov/pubmed/12905141.
5. Houpikian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. *Medicine (Baltimore)*. May 2005;84(3):162-173. Available at http://www.ncbi.nlm.nih.gov/pubmed/15879906.

6. LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TS, Stoler MH. Bacillary angiomatosis. The histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. *The American journal of surgical pathology*. Nov 1989;13(11):909-920. Available at http://www.ncbi.nlm.nih.gov/pubmed/2802010.

7. Regnery RL, Olson JG, Perkins BA, Bibb W. Serological response to "Rochalimaea henselae" antigen in suspected cat-scratch disease. *Lancet*. Jun 13 1992;339(8807):1443-1445. Available at http://www.ncbi.nlm.nih.gov/pubmed/1351130.

8. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother*. Jun 2004;48(6):1921-1933. Available at http://www.ncbi.nlm.nih.gov/pubmed/15155180.

9. Riley LE, Tuomala RE. Bacillary angiomatosis in a pregnant patient with acquired immunodeficiency syndrome. *Obstet Gynecol*. May 1992;79(5 (Pt 2)):818-819. Available at http://www.ncbi.nlm.nih.gov/pubmed/1565376.

10. Kikendall JW, Friedman AC, Oyewole MA, Fleischer D, Johnson LF. Pill-induced esophageal injury. Case reports and review of the medical literature. *Digestive diseases and sciences*. Feb 1983;28(2):174-182. Available at http://www.ncbi.nlm.nih.gov/pubmed/6825537.

11. Maguina C, Garcia PJ, Gotuzzo E, Cordero L, Spach DH. Bartonellosis (Carrion's disease) in the modern era. *Clin Infect Dis*. Sep 15 2001;33(6):772-779. Available at http://www.ncbi.nlm.nih.gov/pubmed/11512081.

Syphilis (Last updated December 17, 2015; last reviewed June 14, 2017)

Epidemiology

Syphilis is associated with an increased risk of sexual acquisition and transmission of HIV.[1-5] In recent years, there has been a resurgence of the disease among men across the United States and in Western Europe (http://www.cdc.gov/std/stats).[6-13] Although coexistent HIV infection (particularly in the advanced stages) may modify the diagnosis, natural history, or management of *Treponema pallidum* infection, the principles of syphilis management remain the same for persons with and without coexistent HIV infection.[14-19]

Clinical Manifestations

The effect of coexistent HIV on the protean manifestations of syphilis have been documented in multiple case reports and small case series, and in a limited number of large studies. In most persons with HIV and syphilis, the clinical manifestations of syphilis are similar to persons without HIV infection. There are some studies that suggest HIV infection may affect the clinical presentation of syphilis, as atypical genital lesions are more apparent, and accelerated progression of syphilis may be seen in persons with advanced immunosupression.[15,16,20,21] Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) count and increase in HIV viral load that improves with recommended syphilis treatment regimens.[19,22-25]

Primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, multiple or atypical chancres occur and primary lesions may be absent or missed in persons with HIV infection.[15,26] Progression to secondary syphilis typically follows 2 to 8 weeks after primary inoculation. The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular, can involve the palms and soles, and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.[16,17,19] Condyloma lata (moist, flat, papular lesions in warm intertrigenous regions) can occur and may resemble condyloma accuminata caused by human papillomavirus. Lues maligna is a rare manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.[27,28] Manifestations of secondary syphilis involving other organs can occur (e.g., hepatitis, nephrotic syndrome, gastritis, pneumonia), however there is no evidence of increased frequency in persons with HIV infection. Constitutional symptoms, along with nonfocal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities such as lymphocytic pleocytosis with a mildly elevated CSF protein, can be seen in secondary syphilis and acute primary HIV infection.[20,21,26,29-32] Signs and symptoms of secondary syphilis can persist from a few days to several weeks before resolving and evolving to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Tertiary syphilis includes cardiovascular syphilis and gummatous syphilis, a slowly progressive disease that can affect any organ system.

Neurosyphilis can occur at any stage of syphilis with different clinical presentations, including cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in persons with HIV infection are similar to those in individuals who do not have HIV infection. However, clinical manifestations of neurosyphilis, such as concomitant uveitis or meningitis, may be more common in persons with HIV infection.[20,21,32-34] A recent clinical advisory has documented increased reports of ocular syphilis, a clinical manifestation of neurosyphilis that often occurs in during early syphilis.[35]

Diagnosis

Darkfield microscopy and tests to detect *T. pallidum* in lesion exudates (e.g., DFA-TP) or tissue (e.g., biopsy with silver stain) are definitive for diagnosing early syphilis. Although *T. pallidum* direct antigen detection tests are no longer commercially available, some laboratories provide locally developed and

validated polymerase chain reaction (PCR) tests for the direct detection of *T. pallidum*. A presumptive serologic diagnosis of syphilis is possible based upon non-treponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and treponemal tests (i.e., fluorescent treponemal antibody absorbed [FTA-ABS], *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence immunoassays [CIA], immunoblots, and rapid treponemal assays).

Serologic diagnosis of syphilis traditionally has involved screening for non-treponemal antibodies with confirmation of reactive tests by treponemal-based assays.[19,36] Some laboratories have initiated a testing algorithm using EIA or CIA as a screening test, followed by a reflex-quantitative, non-treponemal test if the EIA or CIA is positive. This latter strategy may identify those with previously treated syphilis infection, persons with untreated or incompletely treated syphilis, or those with a false positive result in persons with a low likelihood of infection.[37]

In persons with a positive treponemal screening test and a negative reflex-quantitative, non-treponemal test, the laboratory should perform a second treponemal test (based on different antigens from the initial test) to confirm the results of the positive initial treponemal test. If a second treponemal test is positive, persons with a history of previous treatment appropriate for the stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure. In this instance, a repeat non-treponemal test 2 to 4 weeks after the most recent possible exposure is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection (e.g., early stage syphilis), previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative and the risk of syphilis is low, no treatment is indicated.[19,38] Two studies demonstrated that high quantitative index values from treponemal EIA/CIA tests correlated with TP-PA positivity; however, the range of optical density values varies among different treponemal immunoassays, and the clinical significance of these findings warrant further investigation.[39,40] If the risk of syphilis is high (e.g., high risk population or community with high prevalence), a repeat nontreponemal test in 2 to 4 weeks is recommended to evaluate for early infection. In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in persons with a reactive treponemal test and a non-reactive, non-treponemal test;[39,41] examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early-latent syphilis) in persons with HIV infection is identified using the same diagnostic tests used in persons without HIV infection: darkfield microscopy of mucocutaneous lesions and standard serologic tests. Results with VDRL and RPR may be higher, lower (in rare instances), or delayed in persons with HIV infection with early-stage syphilis.[42-46] No data indicate that treponemal tests perform differently among persons with HIV infection,[47] although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.[45,46] Therefore, if serologic tests do not support the diagnosis of syphilis, presumptive treatment is recommended if syphilis is suspected and use of other tests should be considered (e.g., biopsy, darkfield examination, PCR of lesion material, exclusion of prozone phenomenon, repeat serology in 2–4 weeks).

By definition, persons with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) in the absence of clinical manifestations. Early latent syphilis is defined by evidence of infection during the preceding year by

1. A documented seroconversion or four-fold or greater increase in nontreponemal titer; or
2 Symptoms of primary or secondary syphilis; or
3. A sex partner with documented primary, secondary or early latent syphilis.[19]

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All persons with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, altered mental status,) warrant evaluation for neurosyphilis. An immediate ophthalmologic evaluation is recommended for persons with

syphilis and ocular complaints, however a normal CSF evaluation can occur with ocular syphilis. Ocular syphilis should be managed according to the treatment recommendations for neurosyphilis, regardless of CSF results.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early stage syphilis[48] and in persons with HIV infection, even those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early stage syphilis in persons without neurologic symptoms is unknown. Several studies have demonstrated that in persons with syphilis and HIV infection, CSF laboratory abnormalities are associated with CD4 counts ≤350 cells/mm^3 or in combination with RPR titers ≥1:32.[31,32,49,50] However, unless neurologic signs and symptoms are present, a CSF examination has not been associated with improved clinical outcomes.

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count or protein, and a CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. Cerebrospinal fluid (CSF) abnormalities are common in persons with early stage syphilis and are of unknown significance in the absence of neurologic signs or symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm^3), mildly elevated protein concentration, or a reactive CSF-VDRL. Among persons with HIV infection, the CSF leukocyte count can be elevated (>5 white blood cell count [WBC]/mm^3); using a higher cutoff (>20 WBC/ mm^3) might improve the specificity of neurosyphilis diagnosis.[31] In persons with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood), is considered diagnostic of neurosyphilis. If the CSF-VDRL is negative, but serologic tests are reactive, CSF cell count or protein are abnormal, and clinical signs of neurologic involvement are present, treatment for neurosyphilis is recommended. If the neurologic signs and symptoms are nonspecific, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; in the absence of specific neurological signs and symptoms, neurosyphilis is unlikely with a negative CSF FTA-ABS test.[51,52] RPR tests on the CSF have been associated with a high false negative rate and are not recommended.[53] PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

Preventing Exposure and Disease

The resurgence of syphilis in men who have sex with men (MSM) with HIV infection in the United States underscores the importance of primary prevention of syphilis in this population, which should begin with a behavioral risk assessment and routine discussion of sexual behaviors. Health care providers should discuss client-centered risk reduction messages and provide specific actions that can reduce the risk of acquiring sexually transmitted diseases and of transmitting HIV infection.[19,54-58] Routine serologic screening for syphilis is recommended at least annually for all persons with HIV infection who are sexually active, with more frequent screening (i.e., every 3–6 months) for those who have multiple or anonymous partners.[19,59-61] The occurrence of syphilis or any other sexually transmitted infection in a person with HIV infection is an indication of risk behaviors that should prompt intensified risk assessment and counseling messages about the manifestations of syphilis, risk of HIV transmission, and prevention strategies with strong consideration of referral for behavioral intervention.[62] Patients undergoing screening or treatment for syphilis also should be evaluated for other sexually transmitted diseases such as chlamydia and gonorrhea at anatomic sites of exposure in men and for chlamydia, gonorrhea, and trichomonas in women.[19,63]

Preventing Disease

Frequent serologic screening can identify persons recently infected and in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to a partner. Studies in the pre-HIV era demonstrated that approximately one-third of the sex partners of persons who have primary syphilis will develop syphilis within 30 days of exposure, and empiric treatment of incubating syphilis will prevent the development of disease in those who are exposed and onward syphilis transmission

to their partners.[64-67] Those who have had recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively with regimens outlined in current recommendations.

Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AIII)**. Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis more than 90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis. Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings. Sexual partners of infected persons considered at risk of infection should be notified of their exposure and the importance of evaluation.[19] The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation:

- Partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis,
- Partners who have had sexual contact within 6 months plus duration of symptoms for those with secondary syphilis, and
- Partners who have had sexual contact within 1 year for persons with early latent syphilis.

Treating Disease

Treatment regimens for syphilis demonstrate that most persons with HIV infection respond appropriately to single dose benzathine penicillin for primary, secondary, and early latent syphilis.[18,19,43] Closer follow-up is recommended, however, because serologic nonresponse and neurologic complications may be higher in persons with HIV infection.[21,68,69]

Penicillin G remains the treatment of choice for syphilis. Persons with HIV infection with early-stage (e.g., primary, secondary, or early-latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million Units (U) of benzathine penicillin G **(AII)**.[19] The available data demonstrate that high-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.[43] Persons with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin **(AIII)**.

The efficacy of alternative non-penicillin regimens in persons with HIV infection and early syphilis has not been well studied. The use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring. Several retrospective studies support use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis **(BII)**.[70,71] Limited clinical studies, mainly in persons without HIV infection suggest that ceftriaxone, 1 g daily either IM or intravenously (IV) for 10 to 14 days, is effective for treating early stage syphilis **(BII)**, but the optimal dose and duration of therapy have not been defined.[72] A single 2-g oral dose of azithromycin has been shown to be effective for treating early syphilis.[73-75] However *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.[76-81] Azithromycin treatment has not been well studied in persons with HIV infection with early stage syphilis and it should be used with caution in instances when treatment with penicillin or doxycycline is not feasible **(BII)**. Azithromycin has not been studied in pregnant women. Therefore, azithromycin should not be used in MSM or in pregnant women **(AII)**.

In persons with HIV infection who have late latent syphilis, treatment with 3 weekly IM injections of 2.4 million units of benzathine penicillin G is recommended **(AII)**. Alternative therapy is doxycycline, 100 mg

orally twice daily for 28 days, however, it has not been sufficiently evaluated in persons with HIV infection **(BIII)**. Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective; however, the optimal dose and duration of therapy have not been determined.[82,83] If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

Persons with HIV infection who have clinical evidence of tertiary syphilis (i.e., cardiovascular or gummatous disease) should have CSF examination to rule out CSF abnormalities before therapy is initiated. If the CSF evaluation is normal, the recommended treatment of late-stage syphilis is 3 weekly IM injections of 2.4 million U benzathine penicillin G **(AII)**.[19] However, the complexity of tertiary syphilis management, especially cardiovascular syphilis, is beyond the scope of these guidelines and health care providers are advised to consult an infectious disease specialist.

Persons with HIV infection diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million U daily, administered 3 to 4 million U IV every 4 hours or by continuous infusion for 10 to 14 days **(AII)** or procaine penicillin, 2.4 million U IM once daily plus probenecid 500 mg orally 4 times a day for 10 to 14 days **(BII)**.[19,31,32] Persons with HIV infection who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction **(AIII)**. Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such therapy has not been proven beneficial.

Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, 2.4 million U benzathine penicillin IM once per week for up to 3 weeks after completion of neurosyphilis treatment can be considered to provide a comparable duration of therapy **(CIII)**.[19] Desensitization to penicillin is the preferred approach to treating neurosyphilis in patients who are allergic to penicillin. However, limited data indicate that ceftriaxone (2 g daily IV for 10–14 days) may be an acceptable alternative regimen **(BII)**.[83] Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are also available in the 2015 Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines.[19]

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no special considerations regarding the initiation of antiretroviral therapy (ART) in patients with syphilis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome (IRIS) in association with syphilis and treatment with ART in persons with HIV infection is uncommon.[84]

Monitoring and Adverse Events (Including IRIS)

Clinical and serologic responses (four-fold decrease from the nontreponemal titer at the time of treatment) to treatment of early-stage (primary, secondary, and early-latent) disease should be performed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms within 3 to 6 months and seroversion or a fold four decline in nontreponemal titers within 12 to 24 months. Clinical and serologic responses to treatment are similar in persons with HIV infection; subtle variations can occur, however, including a slower temporal pattern of serologic response in persons with HIV infection.[18,19,43,85] Factors associated with the serologic response to treatment in persons without HIV infection include younger age, earlier syphilis stage, and higher RPR titer.[86,87] If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained four-fold increase in non-treponemal titers of greater than 2 weeks, treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for re-infection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% to 20% of persons (including persons with HIV infection) treated with recommended therapy for early stage syphilis will not achieve the four-fold decline in nontreponemal titer used to define treatment response at one year.[19,43] Serum non-treponemal test titers may remain reactive at a stable level (serofast), usually ≤1:8, although rarely may be higher, for prolonged periods. In addition, persons treated for early stage syphilis who have a four-fold decline in titer may not sero-revert to a negative nontreponemal test

and may remain serofast. These serofast states probably do not represent treatment failure.

Response to therapy for late latent syphilis should be monitored using non-treponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a four-fold decline in titer, if initially high (≥1:32), within 12 to 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Most persons with low titers and late latent syphilis remain serofast after treatment often without a four-fold decline in the initial titer. If clinical symptoms develop or a four-fold increase in non-treponemal titers is sustained, then treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for reinfection should be based on the sexual history and risk assessment.[19]

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF-VDRL may respond more slowly. If CSF pleocytosis was present initially, a CSF examination should be repeated at 6 months. Limited data suggest that changes in CSF parameters may occur more slowly in persons with HIV infection, especially with advanced immunosuppression.[20,31] If the cell count has not decreased after 6 months or if the CSF WBC is not normal after 2 years, re-treatment should be considered. In persons on ART with neurosyphilis, declines in serum RPR titers after treatment correlate with normalization of CSF parameters.[88] Use of ART in persons with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment,[20] and a lower risk of developing neurosyphilis.[20]

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache and myalgia that can occur within the first 24 hours after initiation of treatment for syphilis. Antipyretics can be used to manage symptoms but have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction occurs most frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment.[89] Persons with syphilis should be warned about this reaction, instructed how to manage it, and informed it is not an allergic reaction to penicillin.

Managing Possible Treatment Failure or Re-infection

Re-treatment should be considered for persons with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained four-fold increase in serum non-treponemal titers after an initial four-fold decrease following treatment. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment including information about a recent sexual partner with signs or symptoms or recent treatment for syphilis. One study showed that 6% of MSM had a repeat early stage syphilis infection within 2 years of initial infection; HIV infection, Black race, and having multiple sexual partners were associated with increased risk of reinfection.[10] Serologic response should be compared to the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, as definitive criteria for cure or failure have not been well established. Person with HIV infection may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.[19,30,69]

Persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a four-fold increase or greater in titer sustained for more than 2 weeks) and who are at low risk for reinfection should be managed for possible treatment failure. Persons whose non-treponemal titers do not decrease four-fold with 12 to 24 months of therapy can also be managed as a possible treatment failure. Management includes a CSF examination and retreatment with benzathine penicillin G, 2.4 million U at 1-week intervals for 3 weeks **(BIII)**, unless the CSF examination is consistent with CNS involvement. If titers do not respond appropriately after re-treatment, the value of repeated CSF examination or additional therapy is unclear, but it is generally not recommended. Treatment with benzathine penicillin, 2.4 million U IM without a CSF examination unless signs or symptoms of syphilis, and close clinical follow-up can be considered in persons with recurrent signs and symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of syphilis re-infection **(CIII)**.

Persons treated for late latent syphilis should have a CSF examination and be re-treated if they develop clinical signs or symptoms of syphilis or have a sustained four-fold increase in serum non-treponemal test

titer and are low risk for infection; this can also be considered if they experience an inadequate serologic response (i.e., less than four-fold decline in an initially high [≥1:32] non-treponemal test titer) within 12 to 24 months of therapy. If CSF examination is consistent with CNS involvement, re-treatment should follow the recommendations for treatment of neurosyphilis. Persons with a normal CSF examination should be treated with benzathine penicillin 2.4 million U IM weekly for 3 doses **(BIII)**. As with early stage syphilis, the value of repeated CSF examination or additional therapy is unclear, but is generally not recommended. Treatment with benzathine penicillin 2.4 million U IM without a CSF examination unless signs or symptoms of neurosyphilis, and close clinical follow-up can be considered in persons with signs or symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of re-infection **(CIII)**.

Re-treatment for neurosyphilis should be considered if the CSF cell count has not decreased 6 months after completion of treatment or if the CSF cell count or protein is not normal after 2 years.[19]

Preventing Recurrence

No recommendations indicate the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis. Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.[90] Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in persons with HIV infection and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum*.[76-78,80,81] A small pilot study has demonstrated that daily doxycycline prophylaxis was associated with a decreased incidence of syphilis among MSM with HIV infection.[91]

Special Considerations During Pregnancy

Pregnant women should be screened for syphilis at the first prenatal visit. In communities and populations in which the prevalence of syphilis is high and in women at high risk of infection, serologic testing should also be performed twice in the third trimester (ideally at 28–32 weeks gestation) and at delivery.[19] Syphilis screening also should be offered at sites providing episodic care to pregnant women at high risk, including emergency departments, jails, and prisons.[92] Antepartum screening with non-treponemal testing is typical but treponemal screening is being used in some settings. Pregnant women with reactive treponemal screening tests should have additional quantitative testing with non-treponemal tests because titers are essential for monitoring treatment response. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA/CIA tests should be confirmed with a quantitative, non-treponemal test (RPR or VDRL). If the non-treponemal test is negative and the prozone reaction is ruled out, then the results are discordant; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).[93]

No mother or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.[94] All women who have a fetal death after 20 weeks of gestation also should be tested for syphilis.

Rates of transmission to the fetus and adverse pregnancy outcomes for untreated syphilis are highest with primary, secondary, and early-latent syphilis and decrease with increasing duration of infection. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. Concurrent syphilis infection has been associated with increased risk of perinatal transmission of HIV to the infant.[95-100]

Pregnant women with reactive syphilis serology should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the quantitative maternal nontreponemal titer, especially if it ≥1:8. Serofast low antibody titers after documented treatment for the stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and treatment should be considered.[19]

Penicillin is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known

effective antimicrobial for preventing maternal transmission to the fetus and for treatment of fetal infection; however evidence is insufficient to determine the optimal penicillin regimen.[101] There is some evidence to suggest that additional therapy (a second dose of benzathine penicillin G, 2.4 million U IM administered 1 week after the initial dose) may be considered for pregnant women with early syphilis (primary, secondary, and early-latent syphilis) **(BII)**.[19,102,103] Because of concerns about the efficacy of standard therapy in pregnant women who have HIV infection, a second injection in 1 week should also be considered for pregnant women with HIV infection **(BIII)**.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, pregnant women who have a history of penicillin allergy should undergo desensitization and treatment with penicillin **(AIII)**.[19] Erythromycin and azithromycin do not reliably cure maternal or fetal infection **(AII)**; tetracyclines should not be used during pregnancy because of concerns about hepatotoxicity and staining of fetal bones and teeth **(AII)**.[98,104] Data are insufficient on use of ceftriaxone[105] for treatment of maternal infection and prevention of congenital syphilis **(BIII)**.

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if it is associated with a Jarisch-Herxheimer reaction.[106] Pregnant women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement. During the second half of pregnancy, syphilis management can be facilitated with sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis indicate a greater risk of fetal treatment failure.[107] Such cases should be managed in consultation with high-risk obstetric specialists. After 20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

At a minimum, repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy, appropriate for the stage of infection. Data are insufficient on the non-treponemal serologic response to syphilis after stage-appropriate therapy in pregnant women with HIV infection. Non-treponemal titers can be assessed monthly in women at high risk of re-infection. Clinical and non-treponemal antibody titer responses should be appropriate for the stage of disease, although most women will deliver before their serologic response can be definitively assessed. Maternal treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if a woman has clinical signs of infection at delivery, or if the maternal antibody titer is four-fold higher than the pre-treatment titer.[19] The medical provider caring for the newborn should be informed of the mother's serologic and treatment status so that proper evaluation and treatment of the infant can be provided.

Recommendations for Treating *Treponema pallidum* Infections (Syphilis) to Prevent Disease (page 1 of 2)

Empiric treatment of incubating syphilis is recommended to prevent the development of disease in those who are sexually exposed.

Indication for Treatment:

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AIII)**.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain **(AIII)**.

Treatment:

- Same as for early stage syphilis listed below

General Considerations for Treating Syphilis:

- The efficacy of non-penicillin alternatives has not been well evaluated in persons with HIV infection and should be undertaken only with close clinical and serologic monitoring.
- The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment. Patients should be warned about this reaction and informed it is not an allergic reaction to penicillin.

Recommendations for Treating *Treponema pallidum* Infections (Syphilis) to Prevent Disease (page 2 of 2)

Treatment Recommendations Depending on Stage of Disease

Early Stage (Primary, Secondary, and Early-Latent Syphilis)

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM for 1 dose **(AII)**

Alternative Therapy (For Penicillin-Allergic Patients):

- Doxycycline 100 mg PO BID for 14 days **(BII)**, *or*
- Ceftriaxone 1 g IM or IV daily for 10–14 days **(BII)**, *or*
- Azithromycin 2 g PO for 1 dose **(BII)**

Note: Chromosomal mutations associated with azithromycin resistance and treatment failures have been reported, most commonly in MSM. Azithromycin should be used with caution and only when treatment with penicillin, doxycycline or ceftriaxone is not feasible. Azithromycin **is not recommended** for MSM or pregnant women **(AII)**

Note: Persons with penicillin allergy whose compliance or follow-up cannot be ensured and all pregnant women with penicillin allergy should be desensitized and treated with benzathine penicillin.

For pregnant women with early syphilis, a second dose of benzathine penicillin G 2.4 million units IM after one week the single dose treatment may be considered **(BII)**.

Late-Latent (>1 year) or Latent of Unknown Duration

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses **(AII)**

Alternative Therapy (For Penicillin-Allergic Patients):

- Doxycycline 100 mg PO BID for 28 days **(BIII)**

Note: Persons with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin

Late-Stage (Tertiary—Cardiovascular or Gummatous Disease)

- Perform CSF examination to rule out neurosyphilis and obtain infectious diseases consultation to guide management

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses **(AII)**

Neurosyphilis, Otic, or Ocular Disease

Preferred Therapy:

- Aqueous crystalline penicillin G, 18–24 million U per day, administered as 3–4 million U IV q4h or by continuous IV infusion for 10–14 days **(AII)** +/- benzathine penicillin G 2.4 million U IM weekly for 1 to 3 doses after completion of IV therapy **(CIII)**

Alternative Therapy:

- Procaine penicillin G 2.4 million U IM daily plus probenecid 500 mg PO QID for 10–14 days **(BII)** +/- benzathine penicillin G 2.4 million U IM weekly for up to 3 doses after completion of above **(CIII)**
- Persons who are allergic to sulfa-containing medications **should not** be given probenecid, thus the procaine penicillin regimen is not recommended **(AIII)**.

For Penicillin-Allergic Patients:

- Desensitization to penicillin is the preferred approach; if not feasible, ceftriaxone 2 g IM or IV daily for 10–14 days **(BII)**

Key to Acronyms: BID = twice a day; CSF = cerebrospinal fluid; IM = intramuscular; IV = intraveneously; MSM = men who have sex with men; PO = orally; QID = four times a day; q(n)h = every "n" hours; U = Units

References

1. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. Feb 1999;75(1):3-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/10448335.
2. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. Oct 2001;28(10):579-597. Available at http://www.ncbi.nlm.nih.gov/pubmed/11689757.
3. Peterman TA, Newman DR, Maddox L, Schmitt K, Shiver S. High risk for HIV following syphilis diagnosis among men in Florida, 2000-2011. *Public Health Rep*. Mar-Apr 2014;129(2):164-169. Available at http://www.ncbi.nlm.nih.gov/pubmed/24587551.
4. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. Oct 2014;59(7):1020-1026. Available at http://www.ncbi.nlm.nih.gov/pubmed/24928295.
5. Patton ME, Su JR, Nelson R, Weinstock H, Centers for Disease C, Prevention. Primary and secondary syphilis—United States, 2005–2013. *MMWR Morb Mortal Wkly Rep*. May 9 2014;63(18):402-406. Available at http://www.ncbi.nlm.nih.gov/pubmed/24807239.
6. Chesson HW, Sternberg M, Leichliter JS, Aral SO. Changes in the state-level distribution of primary and secondary syphilis in the USA, 1985–2007. *Sex Transm Infect*. Dec 2010;86 Suppl 3:iii58-62. Available at http://www.ncbi.nlm.nih.gov/pubmed/20929854.
7. Torrone EA, Bertolli J, Li J, et al. Increased HIV and primary and secondary syphilis diagnoses among young men—United States, 2004–2008. *J Acquir Immune Defic Syndr*. Nov 1 2011;58(3):328-335. Available at http://www.ncbi.nlm.nih.gov/pubmed/21826012.
8. Kerani RP, Handsfield HH, Stenger MS, et al. Rising rates of syphilis in the era of syphilis elimination. *Sex Transm Dis*. Mar 2007;34(3):154-161. Available at http://www.ncbi.nlm.nih.gov/pubmed/17179773.
9. Buchacz K, Klausner JD, Kerndt PR, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004 to 2005. *J Acquir Immune Defic Syndr*. Feb 1 2008;47(2):234-240. Available at http://www.ncbi.nlm.nih.gov/pubmed/18340654.
10. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002-2006: implications for syphilis elimination efforts. *Am J Public Health*. Jan 2012;102(1):e1-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/22095364.
11. Centers for Disease Control and Prevention. Notes from the field: repeat syphilis infection and HIV coinfection among men who have sex with men—Baltimore, Maryland, 2010–2011. *MMWR Morb Mortal Wkly Rep*. Aug 16 2013;62(32):649-650. Available at http://www.ncbi.nlm.nih.gov/pubmed/23945772.
12. Centers for Disease Control and Prevention. 2012 Sexually Transmitted Disease Surveillance. 2013. Available at http://www.cdc.gov/std/stats12/. Accessed January 7, 2015.
13. Centers for Disease Control and Prevention. Outbreak of syphilis among men who have sex with men--Southern California, 2000. *MMWR Morb Mortal Wkly Rep*. Feb 23 2001;50(7):117-120. Available at http://www.ncbi.nlm.nih.gov/pubmed/11393490.
14. Calza L, Manfredi R, Marinacci G, Tadolini M, Fortunato L, Chiodo F. Efficacy of penicillin G benzathine as antimicrobial treatment of cutaneous secondary syphilis in patients with HIV infection. *J Chemother*. Oct 2002;14(5):533-534. Available at http://www.ncbi.nlm.nih.gov/pubmed/12462435.
15. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW, 3rd. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. *Sex Transm Dis*. Aug 2001;28(8):448-454. Available at http://www.ncbi.nlm.nih.gov/pubmed/11473216.
16. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med*. Dec 1 1990;113(11):872-881. Available at http://www.ncbi.nlm.nih.gov/pubmed/2240901.
17. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to Treponema pallidum antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. *J Am Acad Dermatol*. Feb 1988;18(2 Pt 2):423-428. Available at http://www.ncbi.nlm.nih.gov/pubmed/2963840.

18. Ghanem KG, Workowski KA. Management of adult syphilis. *Clin Infect Dis*. Dec 2011;53 Suppl 3:S110-128. Available at http://www.ncbi.nlm.nih.gov/pubmed/22080265.

19. Workowski KA, Bolan GA, with the Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. Jun 5 2015;64(RR-03):1-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/26042815.

20. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. Jun 19 2008;22(10):1145-1151. Available at http://www.ncbi.nlm.nih.gov/pubmed/18525260.

21. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep*. Jun 29 2007;56(25):625-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/17597693.

22. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. Oct 21 2004;18(15):2075-2079. Available at http://www.ncbi.nlm.nih.gov/pubmed/15577629.

23. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. Jul 2010;10(7):455-463. Available at http://www.ncbi.nlm.nih.gov/pubmed/20610327.

24. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):356-359. Available at http://www.ncbi.nlm.nih.gov/pubmed/17159654.

25. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. *Sex Transm Dis*. Mar 2006;33(3):143-148. Available at http://www.ncbi.nlm.nih.gov/pubmed/16505739.

26. Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. *Sex Transm Dis*. Mar 2001;28(3):158-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/11289198.

27. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS*. Aug 2012;23(8):599-600. Available at http://www.ncbi.nlm.nih.gov/pubmed/22930302.

28. Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis*. Aug 2009;36(8):512-514. Available at http://www.ncbi.nlm.nih.gov/pubmed/19455078.

29. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis. Its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. *Arch Neurol*. Feb 1986;43(2):137-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/3947251.

30. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med*. Jun 18 1987;316(25):1587-1589. Available at http://www.ncbi.nlm.nih.gov/pubmed/3587291.

31. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. Feb 1 2004;189(3):369-376. Available at http://www.ncbi.nlm.nih.gov/pubmed/14745693.

32. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. Apr 1 2004;38(7):1001-1006. Available at http://www.ncbi.nlm.nih.gov/pubmed/15034833.

33. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis*. Jan 2010;37(1):41-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/20118676.

34. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. *Sex Transm Infect*. Feb 2011;87(1):4-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/20798396.

35. Woolston S, Cohen SE, Fanfair RN, Lewis SC, Marra CM, Golden MR. A Cluster of Ocular Syphilis Cases—Seattle, Washington, and San Francisco, California, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(40):1150-1151. Available at http://www.ncbi.nlm.nih.gov/pubmed/26469141.

36. Wicher K, Horowitz HW, Wicher V. Laboratory methods of diagnosis of syphilis for the beginning of the third millennium. *Microbes Infect*. Oct 1999;1(12):1035-1049. Available at http://www.ncbi.nlm.nih.gov/pubmed/10617935.

37. Centers for Disease C, Prevention. Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. Feb 11 2011;60(5):133-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/21307823.

38. Centers for Disease C, Prevention. Syphilis testing algorithms using treponemal tests for initial screening--four laboratories, New York City, 2005-2006. *MMWR Morb Mortal Wkly Rep*. Aug 15 2008;57(32):872-875. Available at http://www.ncbi.nlm.nih.gov/pubmed/18701877.

39. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. *J Infect Dis*. Nov 2011;204(9):1297-1304. Available at http://www.ncbi.nlm.nih.gov/pubmed/21930610.

40. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. *Sex Transm Dis*. Jun 2011;38(6):528-532. Available at http://www.ncbi.nlm.nih.gov/pubmed/21233789.

41. Wohrl S, Geusau A. Neurosyphilis is unlikely in patients with late latent syphilis and a negative blood VDRL-test. *Acta Derm Venereol*. 2006;86(4):335-339. Available at http://www.ncbi.nlm.nih.gov/pubmed/16874420.

42. Rompalo AM, Cannon RO, Quinn TC, Hook EW, 3rd. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. *J Infect Dis*. Jun 1992;165(6):1124-1126. Available at http://www.ncbi.nlm.nih.gov/pubmed/1583332.

43. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*. Jul 31 1997;337(5):307-314. Available at http://www.ncbi.nlm.nih.gov/pubmed/9235493.

44. Augenbraun MH, DeHovitz JA, Feldman J, Clarke L, Landesman S, Minkoff HM. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. *Clin Infect Dis*. Dec 1994;19(6):1040-1044. Available at http://www.ncbi.nlm.nih.gov/pubmed/7888531.

45. Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. A diagnostic dilemma. *Ann Intern Med*. Oct 1987;107(4):492-495. Available at http://www.ncbi.nlm.nih.gov/pubmed/3307583.

46. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. *Arch Dermatol*. Apr 2005;141(4):431-433. Available at http://www.ncbi.nlm.nih.gov/pubmed/15837859.

47. Augenbraun M, Rolfs R, Johnson R, Joesoef R, Pope V. Treponemal specific tests for the serodiagnosis of syphilis. Syphilis and HIV Study Group. *Sex Transm Dis*. Nov 1998;25(10):549-552. Available at http://www.ncbi.nlm.nih.gov/pubmed/9858352.

48. Lukehart SA, Hook EW, 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. *Ann Intern Med*. Dec 1 1988;109(11):855-862. Available at http://www.ncbi.nlm.nih.gov/pubmed/3056164.

49. Libois A, De Wit S, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. *Sex Transm Dis*. Mar 2007;34(3):141-144. Available at http://www.ncbi.nlm.nih.gov/pubmed/16865051.

50. Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. *Clin Infect Dis*. 2009;49:162-163.

51. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med*. Feb 1978;138(2):252-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/343742.

52. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis*. Apr 2012;39(4):291-297. Available at http://www.ncbi.nlm.nih.gov/pubmed/22421696.

53. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. *Sex Transm Dis*. Jun 2012;39(6):453-457. Available at http://www.ncbi.nlm.nih.gov/pubmed/22592831.

54. Rietmeijer CA. Risk reduction counselling for prevention of sexually transmitted infections: how it works and how to make it work. *Sex Transm Infect*. Feb 2007;83(1):2-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/17283359.

55. Force USPST. Behavioral counseling to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. Oct 7 2008;149(7):491-496, W495. Available at http://www.ncbi.nlm.nih.

gov/pubmed/18838729.

56. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA*. Oct 7 1998;280(13):1161-1167. Available at http://www.ncbi.nlm.nih.gov/pubmed/9777816.
57. Richardson JL, Milam J, Stoyanoff S, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S88-94. Available at http://www.ncbi.nlm.nih.gov/pubmed/15385904.
58. Fisher JD, Cornman DH, Osborn CY, Amico KR, Fisher WA, Friedland GA. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: Formative Research, Acceptability, and Fidelity of the Options Project. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S78-87. Available at http://www.ncbi.nlm.nih.gov/pubmed/15385903.
59. Branger J, van der Meer JT, van Ketel RJ, Jurriaans S, Prins JM. High incidence of asymptomatic syphilis in HIV-infected MSM justifies routine screening. *Sex Transm Dis*. Feb 2009;36(2):84-85. Available at http://www.ncbi.nlm.nih.gov/pubmed/18971797.
60. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):1-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/24343580.
61. Centers for Disease C, Prevention, Health R, et al. Recommendations for incorporating human immunodeficiency virus (HIV) prevention into the medical care of persons living with HIV. *Clin Infect Dis*. Jan 1 2004;38(1):104-121. Available at http://www.ncbi.nlm.nih.gov/pubmed/14679456.
62. Guy R, El-Hayek C, Fairley CK, et al. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. *PLoS One*. 2013;8(8):e71436. Available at http://www.ncbi.nlm.nih.gov/pubmed/24009661.
63. Centers for Disease C, Prevention. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. *MMWR Recomm Rep*. Nov 7 2008;57(RR-9):1-83; quiz CE81-84. Available at http://www.ncbi.nlm.nih.gov/pubmed/18987617.
64. Moore MB, Jr., Price EV, Knox JM, Elgin LW. Epidemiologic Treatment of Contacts to Infectious Syphilis. *Public Health Rep*. Nov 1963;78:966-970. Available at http://www.ncbi.nlm.nih.gov/pubmed/14084872.
65. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA*. Nov 1 1971;218(5):711-713. Available at http://www.ncbi.nlm.nih.gov/pubmed/5171497.
66. Schober PC, Gabriel G, White P, Felton WF, Thin RN. How infectious is syphilis? *Br J Vener Dis*. Aug 1983;59(4):217-219. Available at http://www.ncbi.nlm.nih.gov/pubmed/6871650.
67. Hook EW, 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med*. Apr 16 1992;326(16):1060-1069. Available at http://www.ncbi.nlm.nih.gov/pubmed/1549153.
68. Malone JL, Wallace MR, Hendrick BB, et al. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med*. Jul 1995;99(1):55-63. Available at http://www.ncbi.nlm.nih.gov/pubmed/7598143.
69. Walter T, Lebouche B, Miailhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. *Clin Infect Dis*. Sep 15 2006;43(6):787-790. Available at http://www.ncbi.nlm.nih.gov/pubmed/16912958.
70. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. Mar 15 2006;42(6):e45-49. Available at http://www.ncbi.nlm.nih.gov/pubmed/16477545.
71. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. *Am J Med*. Oct 2008;121(10):903-908. Available at http://www.ncbi.nlm.nih.gov/pubmed/18823862.
72. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. Oct 1988;158(4):881-884. Available at http://www.ncbi.nlm.nih.gov/pubmed/3171231.
73. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis*. Jan 2005;32(1):1-6. Available at http://www.ncbi.nlm.nih.gov/pubmed/15614114.
74. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med*. Sep 22 2005;353(12):1236-1244. Available at http://www.ncbi.nlm.nih.gov/

pubmed/16177249.

75. Hook EW, 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis*. Jun 1 2010;201(11):1729-1735. Available at http://www.ncbi.nlm.nih.gov/pubmed/20402591.
76. Centers for Disease C, Prevention. Azithromycin treatment failures in syphilis infections--San Francisco, California, 2002-2003. *MMWR Morb Mortal Wkly Rep*. Mar 12 2004;53(9):197-198. Available at http://www.ncbi.nlm.nih.gov/pubmed/15017376.
77. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. *N Engl J Med*. Jul 8 2004;351(2):154-158. Available at http://www.ncbi.nlm.nih.gov/pubmed/15247355.
78. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. *Clin Infect Dis*. Feb 1 2006;42(3):337-345. Available at http://www.ncbi.nlm.nih.gov/pubmed/16392078.
79. Martin IE, Tsang RS, Sutherland K, et al. Molecular characterization of syphilis in patients in Canada: azithromycin resistance and detection of Treponema pallidum DNA in whole-blood samples versus ulcerative swabs. *J Clin Microbiol*. Jun 2009;47(6):1668-1673. Available at http://www.ncbi.nlm.nih.gov/pubmed/19339468.
80. Wu H, Chang SY, Lee NY, et al. Evaluation of macrolide resistance and enhanced molecular typing of Treponema pallidum in patients with syphilis in Taiwan: a prospective multicenter study. *J Clin Microbiol*. Jul 2012;50(7):2299-2304. Available at http://www.ncbi.nlm.nih.gov/pubmed/22518868.
81. Chen CY, Chi KH, Pillay A, Nachamkin E, Su JR, Ballard RC. Detection of the A2058G and A2059G 23S rRNA Gene Point Mutations Associated with Azithromycin Resistance in Treponema pallidum by Use of a TaqMan Real-Time Multiplex PCR Assay. *J Clin Microbiol*. Mar 2013;51(3):908-913. Available at http://www.ncbi.nlm.nih.gov/pubmed/23284026.
82. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. *Am J Med*. Nov 1992;93(5):481-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/1442850.
83. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS*. May 2004;15(5):328-332. Available at http://www.ncbi.nlm.nih.gov/pubmed/15117503.
84. Bernal E, Munoz A, Ortiz Mdel M, Cano A. Syphilitic panuveitis in an HIV-infected patient after immune restoration. *Enferm Infecc Microbiol Clin*. Oct 2009;27(8):487-489. Available at http://www.ncbi.nlm.nih.gov/pubmed/19406524.
85. Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. *Sex Transm Dis*. 33:151-55. 2006.
86. Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and Serofast State after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis*. Dec 2011;53(11):1092-1099. Available at http://www.ncbi.nlm.nih.gov/pubmed/21998287.
87. Jinno S, Anker B, Kaur P, Bristow CC, Klausner JD. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. *BMC Infect Dis*. 2013;13:605. Available at http://www.ncbi.nlm.nih.gov/pubmed/24369955.
88. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis*. Oct 1 2008;47(7):893-899. Available at http://www.ncbi.nlm.nih.gov/pubmed/18715154.
89. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors. *Clin Infect Dis*. Oct 15 2010;51(8):976-979. Available at http://www.ncbi.nlm.nih.gov/pubmed/20825309.
90. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. Jan 25 2003;361(9354):313-314. Available at http://www.ncbi.nlm.nih.gov/pubmed/12559870.
91. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. Feb 2015;42(2):98-103. Available at http://www.ncbi.nlm.nih.gov/pubmed/25585069.

92. Wolff T, Shelton E, Sessions C, Miller T. Screening for syphilis infection in pregnant women: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. May 19 2009;150(10):710-716. Available at http://www.ncbi.nlm.nih.gov/pubmed/19451578.

93. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant Syphilis Immunoassays in Pregnancy: Perinatal Outcomes and Implications for Clinical Management. *Clin Infect Dis*. Oct 1 2015;61(7):1049-1053. Available at http://www.ncbi.nlm.nih.gov/pubmed/26063719.

94. Genc M, Ledger WJ. Syphilis in pregnancy. *Sex Transm Infect*. Apr 2000;76(2):73-79. Available at http://www.ncbi.nlm.nih.gov/pubmed/10858706.

95. Berman SM. Maternal syphilis: pathophysiology and treatment. *Bull World Health Organ*. Jun 2004;82(6):433-438. Available at http://www.ncbi.nlm.nih.gov/pubmed/15356936.

96. Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS*. Mar 26 1998;12(5):513-520. Available at http://www.ncbi.nlm.nih.gov/pubmed/9543450.

97. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *Int J Gynaecol Obstet*. Dec 1998;63(3):247-252. Available at http://www.ncbi.nlm.nih.gov/pubmed/9989893.

98. Wendel GD, Jr., Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sanchez PJ. Treatment of syphilis in pregnancy and prevention of congenital syphilis. *Clin Infect Dis*. Oct 15 2002;35(Suppl 2):S200-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/12353207.

99. Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. *BJOG*. Jun 2004;111(6):579-584. Available at http://www.ncbi.nlm.nih.gov/pubmed/15198786.

100. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS*. Sep 11 2006;20(14):1869-1877. Available at http://www.ncbi.nlm.nih.gov/pubmed/16954728.

101. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. Cochrane *Database Syst Rev*. 2001(3):CD001143. Available at http://www.ncbi.nlm.nih.gov/pubmed/11686978.

102. Donders GG, Desmyter J, Hooft P, Dewet GH. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegative African women. *Sex Transm Dis*. Feb 1997;24(2):94-101. Available at http://www.ncbi.nlm.nih.gov/pubmed/9111755.

103. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol*. Mar 2002;186(3):569-573. Available at http://www.ncbi.nlm.nih.gov/pubmed/11904625.

104. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol*. Mar 2003;188(3):714-718. Available at http://www.ncbi.nlm.nih.gov/pubmed/12634646.

105. Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis*. Aug 2005;32(8):495-498. Available at http://www.ncbi.nlm.nih.gov/pubmed/16041252.

106. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol*. Mar 1990;75(3 Pt 1):375-380. Available at http://www.ncbi.nlm.nih.gov/pubmed/2304710.

107. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD, Jr. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol*. Jun 2001;97(6):947-953. Available at http://www.ncbi.nlm.nih.gov/pubmed/11384701.

Mucocutaneous Candidiasis (Last updated December 8, 2015; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Oropharyngeal and esophageal candidiasis are common in HIV-infected patients.[1,2] Most such infections are caused by *Candida albicans*. The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.[1,2] In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy, adult women and does not suggest HIV infection. The advent of antiretroviral therapy (ART) has led to a dramatic decline in the prevalence of oropharyngeal and esophageal candidiasis and a marked diminution in cases of refractory disease.

Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly repeated and long-term exposure.[3-5] In this setting, *C. albicans* resistance has been associated with a gradual emergence of non-*albicans Candida* species, particularly *Candida glabrata*, as a cause of refractory mucosal candidiasis in patients with advanced immunosuppression and low CD4 counts.[3,6]

Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, oropharyngeal mucosa, or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis also can be caused by *Candida*. Because a proportion of HIV-infected patients with oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in patients with oropharyngeal candidiasis. Esophageal candidiasis generally presents with retrosternal burning pain or discomfort along with odynophagia; occasionally esophageal candidiasis can be asymptomatic. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease. On occasion, the plaques may progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

In HIV-infected women, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In women with advanced immunosuppression, episodes may be more severe and recur more frequently. In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common and rarely refractory to azole therapy.

Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leukoplakia, the white plaques of oropharyngeal candidiasis can be scraped off the mucosa. If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of *Candida* present.

The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy, or visualization of lesions plus fungal smear or brushings without histopathologic examination. The definitive diagnosis of esophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and confirmation by fungal culture and speciation.

Vulvovaginal candidiasis usually is diagnosed based on the clinical presentation coupled with the demonstration of characteristic blastosphere and hyphal yeast forms in vaginal secretions when examined microscopically after potassium hydroxide preparation. Culture confirmation is rarely required but may provide supportive information. Self-diagnosis of vulvovaginitis is unreliable; microscopic and culture confirmation is required to avoid unnecessary exposure to treatment.

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals. No measures are available to reduce exposure to these fungi.

Preventing Disease

Data from prospective controlled trials indicate that fluconazole can reduce the risk of mucosal disease (i.e., oropharyngeal, esophageal, and vulvovaginal) in patients with advanced HIV.[7-10] However, routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable morbidity and mortality and, moreover, acute therapy is highly effective. Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* species and introduce significant drug-drug interactions. In addition long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII)**.

Treating Disease

Oropharyngeal Candidiasis

Oral fluconazole is as effective or superior to topical therapy for oropharyngeal candidiasis. In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Moreover, oral therapy has the additional benefit over topical regimens in being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy **(AI)**. One to two weeks of therapy is recommended for oropharyngeal candidiasis; two to three weeks of therapy is recommended for esophageal disease.[11]

Using topical agents to treat oropharyngeal candidiasis reduces systemic drug exposure, diminishes risk of drug-drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. Unfavorable taste and multiple daily dosing such as in the cases of clotrimazole and nystatin may lead to decreased tolerability of topical therapy. As an alternative to oral fluconazole, once-daily miconazole in 50-mg mucoadhesive buccal tablets **(BI)** or five-times-per-day clotrimazole troches can be used to treat oropharyngeal candidiasis **(BI)**; these regimens were equivalent as shown in a multicenter, randomized study.[12] Nystatin suspension or pastilles four times daily remains an additional alternative **(BII)**.[13]

Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated **(BI)**.[13] Posaconazole oral suspension[14] is also as effective as fluconazole and generally better tolerated than itraconazole solution **(BI)**. Both antifungals are alternatives to oral fluconazole, although few situations require that these drugs be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.[14] A new solid oral delayed-release tablet formulation of posaconazole is now available.[15] Whether it offers any advantage for the treatment of oropharyngeal candidiasis is unknown and it currently is indicated only for prophylaxis of invasive *Apsergillus* and *Candida* infection.[16] Itraconazole capsules are less effective than fluconazole because of their more variable absorption and they are associated with more drug-drug interactions than fluconazole.

Esophageal Candidiasis

Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**. A 14- to 21-day course of either fluconazole (oral or intravenous [IV]) or oral itraconazole solution is highly effective

(AI). However, patients with severe symptoms initially may have difficulty swallowing oral drugs. As with oropharyngeal candidiasis, itraconazole capsules for esophageal candidiasis are less effective than fluconazole because of variable absorption **(CII)**. Voriconazole, amphotericin B (either deoxycholate or lipid formulations) and the echinocandins caspofungin, micafungin, and anidulafungin all are effective in treating esophageal candidiasis **(BI)**. However, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.[17,18] Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI)**. Although other pathogens (e.g., cytomegalovirus, herpes simplex virus esophagitis) can mimic the symptoms of esophageal candidiasis, a diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. In those who do not respond to antifungal therapy, endoscopy is recommended to identify different causes of esophagitis or drug-resistant *Candida* **(AII)**.

Vulvovaginal Candidiasis

In most HIV-infected women, vulvovaginal candidiasis is uncomplicated and responds readily to short-course oral or topical treatment with any of several therapies, including:

- Oral fluconazole **(AII)**
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) **(AII)**
- Itraconazole oral solution **(BII)**

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥7 days **(AII)**.

Special Considerations with Regard to Starting ART

There are no special considerations regarding initiation of ART in patients with mucocutaneous candidiasis. Specifically, there is as yet no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For most patients with mucocutaneous candidiasis, response to antifungal therapy is rapid; signs and symptoms improve within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although patients may experience cutaneous hypersensitivity reactions characterized by rash and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. Periodic monitoring of liver function studies should be considered if azole therapy is anticipated for >21 days, especially in patients with other hepatic comorbidities **(AII)**. The echinocandins appear to be associated with very few adverse reactions: histamine-related infusion toxicity, transaminase elevations, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.

Immune reconstitution inflammatory syndrome with ART has not yet been reported for mucocutaneous candidiasis in HIV-infected patients. Indeed, ART is associated with a markedly reduced incidence of candidiasis.

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis after 7 to 14 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of HIV-infected patients with oral or esophageal candidiasis, typically those with CD4 cell counts <50 cells/mm^3 and who have received multiple courses of azole antifungals.[4] Confirmatory culture and, in the case of esophageal candidiasis, endoscopy are necessary to confirm treatment failure due to azole resistance or other causes of esophagitis, especially if these procedures were not initially performed.

Posaconazole immediate-release oral suspension (400 mg twice daily for 28 days) is effective in 75% of patients with azole-refractory oropharyngeal or esophageal candidiasis **(AI)**.[19] Again, although the new solid delayed-release tablet formulation has been recently made available, it is not known if it offers an advantage over the suspension for treating this particular disease. Alternatively, oral itraconazole solution is effective, at

least transiently, in approximately two-thirds of patients with fluconazole-refractory mucosal candidiasis **(BII)**.[13] If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII)**, caspofungin **(BII)**, micafungin **(BII)**, or voriconazole **(BII)**.

IV amphotericin B is usually effective for treating refractory disease **(BII)**. Both amphotericin B deoxycholate and the lipid preparations of amphotericin B have been used successfully **(BII)**. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension 4 times daily) is sometimes effective in patients whose oropharyngeal candidiasis does not respond to itraconazole **(BII)**, but this product is not commercially available in the United States.

Preventing Recurrence

When to Start Secondary Prophylaxis

A randomized clinical trial[10] in HIV-infected patients with CD4 counts <150 cells/mm^3 documented a significantly lower number of episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (3 times a week) compared with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two groups among those receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) is not recommended by most HIV specialists for recurrent oropharyngeal or vulvovaginal candidiasis unless patients have frequent or severe recurrences **(BIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for either oropharyngeal **(BI)**, esophageal **(BI)**, or vulvovaginal **(BII)** candidiasis.[7-9] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII)**.[20] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in HIV-infected patients who are severely immunocompromised. Several important factors should be taken into account when making the decision to use secondary prophylaxis. These include the effect of recurrences on the patient's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events and, most importantly, drug-drug interactions.[21]

Rates of relapse are high in patients with azole-refractory oropharyngeal or esophageal candidiasis who have initially responded to echinocandins, voriconazole, or posaconazole therapy. In such patients, secondary prophylaxis should be instituted until ART produces immune reconstitution **(AIII)**.

When to Stop Secondary Prophylaxis

In situations where secondary prophylaxis has been instituted, no data exist to guide recommendations regarding its discontinuation. On the basis of experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has risen to >200 cells/mm^3 following initiation of ART **(AIII)**.

Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same in pregnant women as in those who are not pregnant.

Topical therapy is preferable for treatment of oral or vaginal candidiasis in pregnancy, when possible **(AIII)**. Although single-dose, episodic treatment with oral fluconazole has not been associated with birth defects in humans,[22] its use has not been widely endorsed.[23] Five cases of a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures (fluconazole embryopathy) have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[24] On the basis

of these data, substitution of amphotericin B for high-dose fluconazole in the first trimester is recommended for invasive or refractory esophageal candidal infections **(AIII)**. Neonates born to women receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. Itraconazole has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so these data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[25] but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when given at doses that produced plasma levels equivalent to those seen in humans. Voriconazole is considered a Food and Drug Administration Category D drug because of its association with cleft palate and renal defects seen in rats, as well as embryotoxicity seen in rabbits. However, human data on the use of voriconazole are not available, so use in the first trimester is not recommended. Multiple anomalies have been seen in animals exposed to micafungin, and ossification defects have been seen with use of anidulafungin and caspofungin.[26] Human data are not available for these drugs, thus their use in human pregnancy is not recommended **(AIII)**.

Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles **should not be initiated** during pregnancy **(AIII)**. Furthermore, prophylaxis with systemic azoles **should be discontinued** in HIV-infected women who become pregnant **(AIII)**.

Recommendations for Treating Mucosal Candidiasis (page 1 of 2)

Treating Mucosal Candidiasis

Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 days)

Preferred Oral Therapy:

- Fluconazole 100 mg PO once daily **(AI)**, *or*

Alternative Therapy:

- Clotrimazole troches 10 mg PO 5 times daily **(BI)**, *or*
- Miconazole mucoadhesive buccal tablet 50 mg: Apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet). Refer to product label for more detailed application instructions, **(BI)** *or*
- Itraconazole oral solution 200 mg PO daily **(BI**), *or*
- Posaconazole oral suspension 400 mg PO BID for one day, then 400 mg daily **(BI)**, *or*
- Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily **(BII)**

Esophageal candidiasis (Duration of Therapy: 14–21 days)

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**

Preferred Therapy:

- Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, *or*
- Itraconazole oral solution 200 mg PO daily **(AI)**

Alternative Therapy:

- Voriconazole 200 mg PO or IV BID **(BI)**, *or*
- Caspofungin 50 mg IV daily **(BI)**, *or*
- Micafungin 150 mg IV daily **(BI)**, *or*
- Anidulafungin 100 mg IV for one dose, then 50 mg IV daily **(BI)**, *or*
- Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**, *or*
- Lipid formulation of amphotericin B 3-4 mg/kg IV daily **(BIII)**

Note: A higher rate of esophageal candidiasis relapse has been reported with echinocandins than with fluconazole.

Uncomplicated Vulvovaginal Candidiasis

Preferred Therapy:

- Oral fluconazole 150 mg for 1 dose **(AII)**; *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**

Alternative Therapy:

- Itraconazole oral solution 200 mg PO daily for 3-7 days **(BII)**

Note: Severe or recurrent vaginitis should be treated with oral fluconazole (100–200 mg) or topical antifungals for ≥7 days **(AII)**

Recommendations for Treating Mucosal Candidiasis (page 2 of 2)

Chronic Suppressive Therapy

- Chronic suppressive therapy is usually not recommended unless patients have frequent or severe recurrences **(BIII)**.
- If used, it is reasonable to discontinue therapy if CD4 count >200 cells/mm^3 **(AIII)**.

If Decision Is To Use Suppressive Therapy

Oropharyngeal Candidiasis:

- Fluconazole 100 mg PO once daily or 3 times weekly **(BI)**

Esophageal Candidiasis:

- Fluconazole 100–200 mg PO daily **(BI)**
- Posaconazole oral suspension 400 mg PO BID **(BII)**

Vulvovaginal Candidiasis:

- Fluconazole 150 mg PO once weekly **(BII)**

Other Considerations

- Chronic or prolonged use of azoles might promote development of resistance.
- Systemic azoles may have significant drug-drug interactions with ARV drugs and other drugs for treatment of OI; refer to Table 5 for dosing recommendations. Consider therapeutic drug monitoring if prolonged use is indicated.

Key to Acronyms: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; IV = intravenous; OI = opportunistic infection; PO = orally; QID = four times daily

References

1. Klein RS, Harris CA, Small CB, Moll B, Lesser M, Friedland GH. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Engl J Med*. Aug 9 1984;311(6):354-358. Available at http://www.ncbi.nlm.nih.gov/pubmed/6738653.
2. Bonacini M, Young T, Laine L. The causes of esophageal symptoms in human immunodeficiency virus infection. A prospective study of 110 patients. *Arch Intern Med*. Aug 1991;151(8):1567-1572. Available at http://www.ncbi.nlm.nih.gov/pubmed/1651690.
3. Rex JH, Rinaldi MG, Pfaller MA. Resistance of Candida species to fluconazole. *Antimicrob Agents Chemother*. Jan 1995;39(1):1-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/7695288.
4. Fichtenbaum CJ, Koletar S, Yiannoutsos C, et al. Refractory mucosal candidiasis in advanced human immunodeficiency virus infection. *Clin Infect Dis*. May 2000;30(5):749-756. Available at http://www.ncbi.nlm.nih.gov/pubmed/10816143.
5. Maenza JR, Merz WG, Romagnoli MJ, Keruly JC, Moore RD, Gallant JE. Infection due to fluconazole-resistant Candida in patients with AIDS: prevalence and microbiology. *Clin Infect Dis*. Jan 1997;24(1):28-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/8994752.
6. Martins MD, Lozano-Chiu M, Rex JH. Point prevalence of oropharyngeal carriage of fluconazole-resistant Candida in human immunodeficiency virus-infected patients. *Clin Infect Dis*. Oct 1997;25(4):843-846. Available at http://www.ncbi.nlm.nih.gov/pubmed/9356799.
7. Powderly WG, Finkelstein D, Feinberg J, et al. with the NIAID AIDS Clinical Trials Group. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *N Engl J Med*. Mar 16 1995;332(11):700-705. Available at http://www.ncbi.nlm.nih.gov/pubmed/7854376.
8. Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *Ann Intern Med*. May 1 1997;126(9):689-696. Available at http://www.ncbi.nlm.nih.gov/pubmed/9139554.
9. Havlir DV, Dube MP, McCutchan JA, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. *Clin Infect Dis*. Dec 1998;27(6):1369-1375. Available at http://www.ncbi.nlm.nih.gov/pubmed/9868644.
10. Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic

therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40. *Clin Infect Dis*. Nov 15 2005;41(10):1473-1480. Available at http://www.ncbi.nlm.nih.gov/pubmed/16231260.

11. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. Jan 15 2004;38(2):161-189. Available at http://www.ncbi.nlm.nih.gov/pubmed/14699449.
12. Vazquez JA, Patton LL, Epstein JB, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad(R) efficacy and safety (SMiLES). *HIV Clin Trials*. Jul-Aug 2010;11(4):186-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/20974574.
13. Vazquez JA. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. *HIV AIDS (Auckl)*. 2010;2(1):89-101. Available at http://www.ncbi.nlm.nih.gov/pubmed/22096388.
14. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis*. Apr 15 2006;42(8):1179-1186. Available at http://www.ncbi.nlm.nih.gov/pubmed/16575739.
15. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob Chemother*. Nov 2012;67(11):2725-2730. Available at http://www.ncbi.nlm.nih.gov/pubmed/22833639.
16. Corporation MSD. Posaconazole package insert. 2014. Accessed March 15, 2014.
17. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. *Clin Infect Dis*. Sep 15 2004;39(6):842-849. Available at http://www.ncbi.nlm.nih.gov/pubmed/15472817.
18. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis*. Sep 15 2004;39(6):770-775. Available at http://www.ncbi.nlm.nih.gov/pubmed/15472806.
19. Skiest DJ, Vazquez JA, Anstead GM, et al. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. *Clin Infect Dis*. Feb 15 2007;44(4):607-614. Available at http://www.ncbi.nlm.nih.gov/pubmed/17243069.
20. Vazquez JA, Skiest DJ, Tissot-Dupont H, Lennox JL, Boparai N, Isaacs R. Safety and efficacy of posaconazole in the long-term treatment of azole-refractory oropharyngeal and esophageal candidiasis in patients with HIV infection. *HIV Clin Trials*. Mar-Apr 2007;8(2):86-97. Available at http://www.ncbi.nlm.nih.gov/pubmed/17507324.
21. Marty F, Mylonakis E. Antifungal use in HIV infection. Expert Opin Pharmacother. 2002;3(2):91-102. Available at
22. Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: A systematic review and meta-analysis. *Reprod Toxicol*. Apr 2015;52:78-82. Available at http://www.ncbi.nlm.nih.gov/pubmed/25724389.
23. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. Aug 29 2013;369(9):830-839. Available at http://www.ncbi.nlm.nih.gov/pubmed/23984730.
24. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol*. Nov 2005;73(11):919-923. Available at http://www.ncbi.nlm.nih.gov/pubmed/16265639.
25. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.
26. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. *J Antimicrob Chemother*. Jan 2015;70(1):14-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/25204341.

Invasive Mycoses

Introduction (Last updated December 22, 2015; last reviewed December 22, 2015)

The fungal infections to be discussed in this section include cryptococcosis, histoplasmosis, and coccidioidomycosis. Candidiasis and pneumocystosis are discussed in other sections of this document. Blastomycosis, penicilliosis, and paracoccidioidomycosis are not discussed because their current incidence as opportunistic infections among patients with HIV-1 infection in the United States is very low. In addition, aspergillosis is no longer addressed in these guidelines because of the low incidence of this mycosis among HIV-infected persons without other underlying risk factors and the management of aspergillosis is otherwise similar to that in persons with other immunodeficiencies.

Cryptococcosis (Last updated August 17, 2016; last reviewed June 14, 2017)

Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the etiology. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of HIV-infected patients in developed countries were diagnosed with disseminated cryptococcosis.[1] Current estimates indicate that every year, nearly 1 million cases of cryptococcal meningitis are diagnosed worldwide and the disease accounts for more than 600,000 deaths.[2] With the availability of effective ART, the incidence of the disease has declined substantially in areas with ART access, and most new infections are being recognized in patients recently diagnosed with HIV infection.[3] Most cases are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/μL.

Clinical Manifestations

In HIV-infected patients, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache.[1] Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure.

Cryptococcosis usually is disseminated when diagnosed in an HIV-infected patient. Any organ of the body can be involved, and skin lesions may show myriad different manifestations, including umbilicated skin lesions mimicking molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and mimic *Pneumocystis* pneumonia.

Diagnosis

Analysis of cerebrospinal fluid (CSF) generally demonstrates mildly elevated levels of serum protein, low-to-normal glucose concentrations, and pleocytosis consisting mostly of lymphocytes. Some HIV-infected patients will have very few CSF inflammatory cells, but a Gram's stain preparation, or an India ink preparation if available, may demonstrate numerous yeast forms. The opening pressure in the CSF may be elevated, with pressures ≥25 cm H_2O occurring in 60% to 80% of patients.[4,5]

Cryptococcal disease can be diagnosed through culture, CSF microscopy, or by cryptococcal antigen (CrAg) detection. In patients with HIV-related cryptococcal meningitis, 55% of blood cultures and 95% of CSF cultures are positive and visible colonies can be detected within 7 days. Cryptococcus may be occasionally

identified on a routine Gram stain preparation of CSF. India ink staining of CSF demonstrates encapsulated yeast in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infections and may be present weeks to months before symptom onset.[6] A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. Three methods exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test). Testing for the antigen in the serum is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients,[7] and it may be particularly useful when a lumbar puncture is delayed or refused.

Preventing Exposure

Cryptococcus is ubiquitous in the environment. HIV-infected patients cannot completely avoid exposure to *C. neoformans* or *C. gattii*. Limited epidemiological evidence suggests that exposure to aged bird droppings may increase risk of infection.

Preventing Disease

The incidence of cryptococcal disease is low among HIV-infected patients in the United States. However, a recent report from the United States indicates that among HIV-infected patients with peripheral blood CD4 counts ≤100 cells/μL, the prevalence of cryptococcal antigenemia, a harbinger of disease, was 2.9%, and prevalence was 4.3% for those with CD4 counts ≤50 cells/μL.[8] Routine testing for serum CrAg in newly diagnosed HIV-infected persons with no overt clinical signs of meningitis is recommended by some experts for patients whose CD4 counts are ≤100 cells/μL and particularly in those with CD4 counts ≤50 cells/μL. A positive test should prompt CSF evaluation for meningitis.

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients who have CD4 counts <100 cells/μL.[9,10] However, in the United States, primary prophylaxis in the absence of a positive serum cryptococcal antigen test is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost **(BII)**. Patients with isolated cryptococcal antigenemia without meningitis can be treated similarly to patients with focal pulmonary cryptococcosis (see below).

Treating Disease

Treating cryptococcosis consists of three phases: induction, consolidation, and maintenance therapy. For induction treatment for cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously, in combination with oral flucytosine, is recommended **(AI)**. Historically, amphotericin B deoxycholate has been the preferred formulation at a dose of 0.7 to 1.0 mg/kg daily. However, there is a growing body of evidence that lipid formulations of amphotericin B are effective for disseminated cryptococcosis, particularly in patients who experience clinically significant renal dysfunction during therapy or who are likely to develop it. The non-comparative CLEAR study demonstrated a 58% response rate in HIV-infected patients treated with amphotericin B lipid complex at mean dose of 4.4 mg/kg daily.[11] In a Dutch and Australian study, a 3-week course of liposomal amphotericin B (4 mg/kg daily) resulted in more rapid sterilization of CSF than amphotericin B deoxycholate (0.7 mg/kg daily).[12] A recently published comparison of amphotericin B deoxycholate (0.7 mg/kg daily), and liposomal amphotericin B (AmBisome®) (3 mg/kg or 6 mg/kg daily) showed similar efficacy for the three regimens, but nephrotoxicity was lower with 3 mg/kg daily liposomal amphotericin B.[13]

Amphotericin B formulations should be combined with flucytosine at a dose of 100 mg/kg daily in 4 divided doses for ≥2 weeks in patients with normal renal function, and this is the preferred regimen for primary induction therapy **(AI)**. Based on available clinical trial data, a daily dose of 3 to 4 mg/kg of liposomal

amphotericin B is the recommended amphotericin B formulation **(AI)**. Amphotericin B deoxycholate at a dose of 0.7 mg/kg daily is equally efficacious **(AI)** and can be used if cost is an issue and the risk of renal dysfunction is low. Amphotericin B lipid complex at a dose of 5 mg/kg daily can be used as an alternative amphotericin B preparation, although fewer data are available to support its use **(BII)**.

When using flucytosine, serum levels of flucytosine, if this assay is available, should be obtained 2 hours post-dose after 3 to 5 doses have been administered. Serum levels should be between 25 and 100 mg/L.[16] Renal function should be monitored closely and the flucytosine dose adjusted accordingly for patients with renal impairment. The dose of flucytosine should be reduced by 50% for every 50% decline in creatinine clearance. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF.[14-17] A recent randomized clinical trial also showed that the combination of amphotericin B deoxycholate at a dose of 1.0 mg/kg daily combined with flucytosine was associated with improved survival compared to the same dose of amphotericin B without flucytosine.[18]

Amphotericin B deoxycholate in combination with 400 mg of fluconazole daily was inferior to amphotericin B in combination with flucytosine for clearing *Cryptococcus* from CSF.[19] However, in 2 randomized trials, amphotericin B plus 800 mg of fluconazole daily compared favorably with amphotericin B alone.[19,20] Therefore, amphotericin B deoxycholate alone or combined with fluconazole at 800 mg daily **(BI)** or lipid-formulation amphotericin B alone or combined with fluconazole at 800 mg daily **(BIII)** may be viable options in some circumstances but are less preferable alternatives than lipid-formulation amphotericin B combined with flucytosine **(BI)**.

Fluconazole (400 mg daily) combined with flucytosine is also a potential alternative to amphotericin B regimens **(BII)**.[21] Some experts would use 800 mg daily **(BIII)**. Fluconazole alone, based on early fungicidal activity, is inferior to amphotericin B[22] for induction therapy and is recommended only for patients who cannot tolerate or do not respond to standard treatment. If it is used for primary induction therapy, the starting daily dose should be 1200 mg **(CI)**.[23]

After at least 2 weeks of successful induction therapy—defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture—amphotericin B and flucytosine can be discontinued and follow-up or consolidation therapy initiated with fluconazole at 400 mg daily **(AI)**. This therapy should continue for at least 8 weeks **(AI)**.[14,15,24] Subsequently, the fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least 1 year of azole therapy (see the Preventing Recurrence section below).[25] Itraconazole, at the same dosage as fluconazole, can be used as an alternative **(CI)**, but it is clearly inferior to fluconazole.[24] Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or maintenance therapy for patients with cryptococcosis. Most of the data on use of these extended-spectrum triazole antifungals have been reported for treatment of refractory cases, with success rates of approximately 50%.[26,27] At this time, the role of posaconazole and voriconazole in the management of cryptococcosis is not established. Voriconazole should be used cautiously with HIV protease inhibitors and efavirenz.

Non-central-nervous-system (CNS), extrapulmonary cryptococcosis, and diffuse pulmonary disease should be treated similarly to CNS disease **(BIII)**. For mild-to-moderate symptoms and focal pulmonary infiltrates, treatment with fluconazole (400 mg daily for 12 months) combined with effective ART is appropriate **(BIII)**. Treatment is the same for patients with an isolated positive serum cryptococcal antigen test **(BIII)**. **All patients should have their CSF sampled to rule out CNS disease.**

Special Considerations with Regard to Starting ART

Optimal timing for ART initiation in patients with acute cryptococcal meningitis is controversial. One randomized, controlled trial that included 35 patients with cryptococcal meningitis suggested that ART was safe when started within the first 14 days of diagnosis.[28] A subsequent study from Africa demonstrated significantly worse outcomes in 54 patients started on ART within 72 hours of cryptococcal meningitis diagnosis compared with those in which ART was delayed for at least 10 weeks.[29] However, in the latter study, cryptococcal meningitis was managed with fluconazole alone, and ART consisted of nevirapine, stavudine, and lamivudine.

Neither fluconazole alone nor the latter ART regimen are recommended as preferred initial treatment in the United States. A randomized clinical trial conducted at 2 sites in Africa among hospitalized patients with acute cryptococcal meningitis[30] compared patients with cryptococcal meningitis who were started on ART within 1 to 2 weeks (median 8 days) after fungal diagnosis with patients in whom ART was deferred until 5 weeks (median 36 days) after diagnosis. In contrast to the other African study, this study used deoxycholate amphotericin B (0.7–1.0 mg/kg daily) plus 800 mg of fluconazole daily during the induction phase of antifungal treatment. There was a significant increase in 6-month mortality in the early ART group compared with the deferred ART group (45% vs 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of study ($P = 0.007$). The difference in mortality was even greater between the early ART group and the deferred ART group if the CSF white cell count was <5 cells/μL ($P = 0.008$). While the excess of deaths in the early ART group was attributed to cryptococcosis, it is unclear if they were directly due to meningitis and its sequelae or due to immune reconstitution inflammatory syndrome (IRIS).

Based on the studies cited above and on expert opinion, it is prudent to delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. Delay in ART may be particularly important in those with evidence of increased intracranial pressure or in those with low CSF white blood cell counts. Hence, the timing of ART administration should be considered between 2 and 10 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions and local experience **(BIII)**. If effective ART is to begin prior to 10 weeks, the treating physicians should be prepared to aggressively address complications caused by IRIS, such as elevated intracranial pressure (ICP).

For other forms of cryptococcosis, where the risk of IRIS appears to be much lower, the optimal time to begin ART and antifungal therapy is not clear. However, it would seem prudent to delay initiation of ART by 2 to 4 weeks after starting antifungal therapy **(BIII)**.

All the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

ICP elevations can cause clinical deterioration despite a microbiologic response, and they are more likely to occur if the CSF opening lumbar pressure is ≥25cm H_2O[4,14] when obtained in the lateral decubitus position with good manometrics assured. In 1 large clinical trial, increased ICP was associated with 93% of deaths during the first 2 weeks of therapy and 40% of deaths during weeks 3 to 10.[4] Although it is uncertain which patients with high opening lumbar pressures will deteriorate, those with symptoms and signs of ICP require immediate clinical intervention.

Lumbar opening pressure should be measured in all patients with cryptococcal meningitis at the time of diagnosis. Measures to decrease ICP should be used for all patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased pressure. Drainage of CSF via lumbar puncture is recommended for initial management. One approach is to remove a volume of CSF (typically 20–30 mL) that at least halves the opening pressure[31] and repeat daily until symptoms and signs consistently improve. CSF shunting through a lumbar drain or ventriculostomy should be considered for patients who cannot tolerate repeated lumbar punctures or in whom signs and symptoms of cerebral edema persist after multiple lumbar taps **(BIII)**. Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended** **(AIII)**. Acetazolamide **should not be used** as therapy for increased ICP management since it may cause hyperchloremic acidosis and does not result in a decrease in ICP **(AI)**.[32] A randomized study compared a 6-week course of a tapering dose of dexamethasone among 451 Asian and African patients with HIV infection and cryptococcal meningitis who received amphotericin B deoxycholate plus fluconazole as the induction antifungal regimen. Compared to those receiving placebo, there was no improvement in survival at 10 weeks and dexamethasone was associated with more adverse

events.[33] These data support the recommendation that corticosteroids should not routinely be used during induction therapy for HIV-associated cryptococcal meningitis unless they are being used for IRIS **(AI)**.

After the first 2 weeks of treatment, many experts would advocate a repeat lumbar puncture to ensure that viable organisms have been cleared from the CSF. Even in patients who have clinical improvement, positive CSF cultures after 2 weeks of therapy are predictive of future relapse and less favorable outcomes. In such cases, some experts would continue amphotericin B plus flucytosine until the CSF cultures are negative **(BIII)**. Monitoring titers of cryptococcal polysaccharide antigen in serum or CSF is of no value in determining response to therapy and **is not recommended**. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening lumbar pressure and CSF culture, should be performed.

Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline appears to reduce the risk of nephrotoxicity during amphotericin B treatment. Thirty minutes before infusion, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered in an attempt to ameliorate infusion-related adverse reactions **(BIII)**, but data supporting these practices are scant. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B-associated rigors **(BII)**.

In patients receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine levels. Peak serum flucytosine levels should be obtained 2 hours after an oral dose and the therapeutic range is between 25 and 100 mg/L. Alternatively, frequent (i.e., at least biweekly) blood counts can be performed to detect development of cytopenia. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

An estimated 30% of HIV-infected patients with cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART.[34,35] Patients who have cryptococcal IRIS are more likely to be antiretroviral naive, have higher HIV RNA levels, and have less CSF inflammation on initial presentation.[36] The risk of IRIS may be decreased in those with negative CSF cultures at the time of antiretroviral initiation.[37] Distinguishing IRIS from treatment failure may be difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite microbiological evidence of effective antifungal therapy,[36,38] whereas treatment failure is associated with continued positive cultures. The appropriate management strategy for IRIS is to continue both ART and antifungal therapy and reduce elevated ICP, if present **(AII)**. In patients with severe symptoms of IRIS, some specialists recommend a brief course of glucocorticosteroids **(CIII)**, but data-based management strategies have not been developed.

The risk of IRIS appears to be much lower with other forms of cryptococcosis; IRIS may present as lymphadenitis, cutaneous abscesses, or bony lesions.[39] Management is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII)**, and considering glucocorticoids **(CIII)**.

Managing Treatment Failure

Treatment failure is defined as a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy, including management of increased ICP; or as a relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Direct primary fluconazole resistance with *C. neoformans* has been reported in the United States but is uncommon.[40] Therefore, susceptibility testing is not routinely recommended for intial management of cryptococcosis. Isolates collected to evaluate for persistence or relapse should, however, be checked for susceptibility and compared with the original isolate. While clinical data are lacking, strains with minimum inhibitory concentrations against fluconazole ≥16 µg/mL in patients with persistent disease or relapse may be considered resistant.[41]

Optimal therapy for patients with treatment failure has not been established. Patients who fail to respond to induction with fluconazole monotherapy should be switched to amphotericin B, with or without flucytosine. Those initially treated with an amphotericin B formulation should remain on it until a clinical response occurs. Liposomal amphotericin B (4–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is

better tolerated and has greater efficacy than deoxycholate formulation in this setting[12,13,42] and should be considered when initial treatment with other regimens fails **(AII)**.

Higher doses of fluconazole in combination with flucytosine also may be useful **(BIII)**. Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis **(AII)**. The newer triazoles—posaconazole and voriconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy, but probably offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates fluconazole resistance. Most clinical failures are a result of inadequate induction therapy, drug interactions that interfere with treatment, or the development of IRIS and are not due to drug resistance.

Preventing Recurrence

When to Start Chronic Suppressive Therapy

Patients who have completed the first 10 weeks of induction and consolidation therapy for acute cryptococcosis should be given chronic maintenance or suppressive therapy with 200 mg of fluconazole daily **(AI)**. Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease **(CI)**.[24]

When to Stop Chronic Suppressive Therapy

Only a small number of patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of secondary prophylaxis while on ART. In a European study, recurrence of cryptococcosis was not seen among 39 subjects on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 cell count was 297 cells/μL, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[43] A prospective, randomized study of 60 patients in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after having achieved a CD4 count >100 cells/μL with a sustained undetectable HIV RNA level for 3 months on potent ART.[44] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue chronic antifungal maintenance therapy for cryptococcosis in patients whose CD4 cell counts are ≥100 cells/μL, who have undetectable viral loads on ART for >3 months, and who have received a minimum of 1 year of azole antifungal chronic maintenance therapy after successful treatment of cryptococcosis **(BII)**.[45] Secondary prophylaxis should be reinitiated if the CD4 count decreases again to <100 cells/μL **(AIII)**.

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections during pregnancy is similar to that in non-pregnant adults. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that the postpartum period may be a high-risk period for the development of IRIS.

Lipid formulations of amphotericin B are the preferred initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Flucytosine was teratogenic in animal studies, and human experience is limited to case reports and small series. Therefore, its use should be considered only when the benefits outweigh its risks to the fetus **(CIII)**.

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg/day or more through or beyond the first trimester of pregnancy.[46] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short-term exposure to fluconazole.[47,48] Based on the reported birth defects, the FDA has changed the

pregnancy category for fluconazole from C to D for any use other than a single, low dose for treatment of vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh risks. For pregnant women, amphotericin should be continued throughout the first trimester. After the first trimester, switching to oral fluconazole may be considered, if clinically appropriate.

Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[49,50] However, in general azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Treating Cryptococcosis (page 1 of 2)

Treating Cryptococcal Meningitis

Treatment for cryptococcosis consists of 3 phases: induction, consolidation, and maintenance therapy.

Induction Therapy (For At Least 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens:

- Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(AI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(AI)**—if cost is an issue and the risk of renal dysfunction is low

Note: Flucytosine dose should be adjusted in renal impairment (see Table 7).

Alternative Regimens:

- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(BII)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800 mg PO or IV daily **(BIII)**; *or*
- Amphotericin B (deoxycholate 0.7-1.0 mg/kg IV daily) plus fluconazole 800 mg PO or IV daily **(BI)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily alone **(BI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily alone **(BI)**; *or*
- Fluconazole 400 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BII)**; *or*
- Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BIII)**; *or*
- Fluconazole 1200 mg PO or IV daily alone **(CI)**

Consolidation Therapy (For At Least 8 Weeks, Followed by Maintenance Therapy)

- To begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat LP)

Preferred Regimen:

- Fluconazole 400 mg PO or IV once daily **(AI)**

Alternative Regimen:

- Itraconazole 200 mg PO BID **(CI)**

Maintenance Therapy

Preferred Regimen:

- Fluconazole 200 mg PO for at least 1 year **(AI)**—see below for recommendation of when to stop maintenance therapy

Stopping Maintenance Therapy

*If the Following Criteria are Fulfilled **(BII)**:*

- Completed initial (induction, consolidation) therapy, and at least 1 year on maintenance therapy, *and*

Recommendations for Preventing and Treating Cryptococcosis (page 2 of 2)

- Remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥100 cells/μL for ≥3 months and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy:

- If CD4 count declines to ≤100 cells/μL **(AIII)**

Treating Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease:

- Same treatment as for CNS disease **(BIII)**

Treating Non-CNS Cryptococococcosis Focal Pulmonary Disease and Isolated Cryptococcal Antigenemia:

- Fluconazole 400 mg PO daily for 12 months **(BIII)**

Other Considerations:

- Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.
- When flucytosine is used, serum levels (if available) should be monitored (2 hours post-dose, after 3–5 doses) and drug concentration should be between 25–100 mg/L).
- Opening pressure should always be measured when a LP is performed. Repeated LPs or CSF shunting are essential to effectively manage symptomatic increased ICP.
- In a randomized, controlled trial, a 6-week course of tapering doses of dexamethasone as adjunctive therapy for cryptococcal meningitis did not improve 10-week survival when compared to placebo, and resulted in a higher rate of adverse events. Corticosteroids should not be routinely used during induction therapy unless it is used for management of IRIS **(AI)**.
- Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**.
- Infection due to *C. gattii* should be treated similarly to *C. neoformans* **(BIII)**.
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous; LP = lumbar puncture; PO = orally; QID = four times a day

References

1. Aberg J, WG. P. Cryptococcosis. In: Dolin R MH, Saag MS, ed. *AIDS Therapy*. New York, NY: Churcill Livingstone; 2002:498-510.
2. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. Feb 20 2009;23(4):525-530. Available at http://www.ncbi.nlm.nih.gov/pubmed/19182676.
3. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis*. Mar 15 2003;36(6):789-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/12627365.
4. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis*. Jan 2000;30(1):47-54. Available at http://www.ncbi.nlm.nih.gov/pubmed/10619732.
5. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS*. Mar 27 2009;23(6):701-706. Available at http://www.ncbi.nlm.nih.gov/pubmed/19279443.
6. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*. May 3 2002;16(7):1031-1038. Available at http://www.ncbi.nlm.nih.gov/pubmed/11953469.
7. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis*. May 1994;18(5):789-792. Available at http://www.ncbi.nlm.nih.gov/pubmed/8075272.

8. McKenney J, Bauman S, Neary B, et al. Prevalence, correlates, and outcomes of cryptococcal antigen positivity among patients with AIDS, United States, 1986-2012. *Clin Infect Dis*. Mar 15 2015;60(6):959-965. Available at http://www.ncbi.nlm.nih.gov/pubmed/25422390.

9. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. Mar 16 1995;332(11):700-705. Available at http://www.ncbi.nlm.nih.gov/pubmed/7854376.

10. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. May 1999;28(5):1049-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452633.

11. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis*. May 1 2005;40 Suppl 6:S409-413. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809927.

12. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. Oct 1997;11(12):1463-1471. Available at http://www.ncbi.nlm.nih.gov/pubmed/9342068.

13. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis*. Jul 15 2010;51(2):225-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/20536366.

14. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. Jul 3 1997;337(1):15-21. Available at http://www.ncbi.nlm.nih.gov/pubmed/9203426.

15. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis*. Apr 2000;30(4):710-718. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770733.

16. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O, French Cryptococcosis Study G. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. Feb 2007;4(2):e21. Available at http://www.ncbi.nlm.nih.gov/pubmed/17284154.

17. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study G. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One*. 2008;3(8):e2870. Available at http://www.ncbi.nlm.nih.gov/pubmed/18682846.

18. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. Apr 4 2013;368(14):1291-1302. Available at http://www.ncbi.nlm.nih.gov/pubmed/23550668.

19. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet*. May 29 2004;363(9423):1764-1767. Available at http://www.ncbi.nlm.nih.gov/pubmed/15172774.

20. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis*. Jun 15 2009;48(12):1775-1783. Available at http://www.ncbi.nlm.nih.gov/pubmed/19441980.

21. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis*. Oct 1994;19(4):741-745. Available at http://www.ncbi.nlm.nih.gov/pubmed/7803641.

22. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. Jul 1 2007;45(1):76-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/17554704.

23. Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis*.

Feb 1 2010;50(3):338-344. Available at http://www.ncbi.nlm.nih.gov/pubmed/20038244.

24. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. Feb 1999;28(2):291-296. Available at http://www.ncbi.nlm.nih.gov/pubmed/10064246.
25. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *N Engl J Med*. Mar 19 1992;326(12):793-798. Available at http://www.ncbi.nlm.nih.gov/pubmed/1538722.
26. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. May 1 2003;36(9):1122-1131. Available at http://www.ncbi.nlm.nih.gov/pubmed/12715306.
27. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother*. Oct 2005;56(4):745-755. Available at http://www.ncbi.nlm.nih.gov/pubmed/16135526.
28. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/pubmed/19440326.
29. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis*. Jun 1 2010;50(11):1532-1538. Available at http://www.ncbi.nlm.nih.gov/pubmed/20415574.
30. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. Jun 26 2014;370(26):2487-2498. Available at http://www.ncbi.nlm.nih.gov/pubmed/24963568.
31. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association*. Feb 1 1998;17(2):137-142. Available at http://www.ncbi.nlm.nih.gov/pubmed/9473014.
32. Newton PN, Thai le H, Tip NQ, et al. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis*. Sep 15 2002;35(6):769-772. Available at http://www.ncbi.nlm.nih.gov/pubmed/12203177.
33. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *N Engl J Med*. Feb 11 2016;374(6):542-554. Available at http://www.ncbi.nlm.nih.gov/pubmed/26863355.
34. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Apr 1 2005;40(7):1049-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/15825000.
35. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. Apr 2010;10(4):251-261. Available at http://www.ncbi.nlm.nih.gov/pubmed/20334848.
36. Boulware DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis*. Sep 15 2010;202(6):962-970. Available at http://www.ncbi.nlm.nih.gov/pubmed/20677939.
37. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Aug 24 2013;27(13):2089-2099. Available at http://www.ncbi.nlm.nih.gov/pubmed/23525034.
38. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. Nov 2010;10(11):791-802. Available at http://www.ncbi.nlm.nih.gov/pubmed/21029993.
39. Kuttiatt V, Sreenivasa P, Garg I, Shet A. Cryptococcal lymphadenitis and immune reconstitution inflammatory syndrome: current considerations. *Scand J Infect Dis*. Aug 2011;43(8):664-668. Available at http://www.ncbi.nlm.nih.gov/pubmed/21534892.
40. Brandt ME, Pfaller MA, Hajjeh RA, et al. Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates in the United States: 1992 to 1994 and 1996 to 1998. *Antimicrob Agents Chemother*. Nov 2001;45(11):3065-3069.

Available at http://www.ncbi.nlm.nih.gov/pubmed/11600357.

41. Witt MD, Lewis RJ, Larsen RA, et al. Identification of patients with acute AIDS-associated cryptococcal meningitis who can be effectively treated with fluconazole: the role of antifungal susceptibility testing. *Clin Infect Dis*. Feb 1996;22(2):322-328. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838190.
42. Chen SC, Australasian Society for Infectious Diseases Mycoses Iterest G. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother*. Feb 2002;49 Suppl 1(Suppl 1):57-61. Available at http://www.ncbi.nlm.nih.gov/pubmed/11801583.
43. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med*. Aug 20 2002;137(4):239-250. Available at http://www.ncbi.nlm.nih.gov/pubmed/12186514.
44. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clin Infect Dis*. May 15 2003;36(10):1329-1331. Available at http://www.ncbi.nlm.nih.gov/pubmed/12746781.
45. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis*. Feb 15 2004;38(4):565-571. Available at http://www.ncbi.nlm.nih.gov/pubmed/14765351.
46. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.
47. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at http://www.ncbi.nlm.nih.gov/pubmed/18400803.
48. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at http://www.ncbi.nlm.nih.gov/pubmed/8987954.
49. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.
50. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.

Histoplasmosis (Last updated May 7, 2013; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Infection is endemic to the central and south-central United States and is especially common in the Ohio and Mississippi River Valleys. It is also endemic in Latin America, including Puerto Rico. In endemic areas, annual incidence approaches 5% in HIV-infected individuals. A CD4 T lymphocyte (CD4) count <150 cells/mm^3 is associated with an increased risk of symptomatic illness.[1,2]

Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia that form in the mycelial phase. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. When cellular immunity wanes, reactivation of a silent focus of infection that was acquired years earlier can occur, and it is the presumed mechanism for disease occurrence in nonendemic areas. Incidence of symptomatic histoplasmosis in HIV-infected patients appears to have declined with the advent of effective antiretroviral therapy (ART). When histoplasmosis does occur, however, it is reported as the AIDS-defining illness in 25% to 61% of patients.[3,4]

Clinical Manifestations

In HIV-infected patients, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnea occur in approximately 50% of patients.[1,4] Central nervous system (CNS), gastrointestinal, and cutaneous manifestations occur in a smaller percentage, although in a series from Panama, diarrhea occurred in 50% of patients.[5] Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and also (if brain involvement is present) seizures, focal neurological deficits, and changes in mental status.[6] Gastrointestinal disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.[7] For patients whose CD4 counts are >300 cells/mm^3, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis and acute pulmonary histoplasmosis[8] but is insensitive for chronic forms of pulmonary infection. Using a newer quantitative assay, antigen was detected in the urine of 100% and in the serum of 92% of AIDS patients with disseminated histoplasmosis.[9] Antigen detection in bronchoalveolar lavage fluid appears to be a useful method for diagnosis of pulmonary histoplasmosis.[10] In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells. Histopathological examination of biopsy material from involved tissues demonstrates the characteristic 2 to 4 µm budding yeast and can provide a rapid diagnosis.

H. capsulatum can be cultured from blood, bone marrow, respiratory secretions, or other involved sites in >85% of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.[11] Serologic tests are less useful than antigen assays in AIDS patients with disseminated histoplasmosis but may be helpful in patients who have reasonably intact immune responses with pulmonary disease.[11,12]

The diagnosis of meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are a lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[6] However, *Histoplasma* antigen or antibodies against *H. capsulatum* can be detected in CSF in up to 70% of cases, and a positive result for either test is diagnostic. For some patients, none of these specific tests is positive, and a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not explained by another cause.

Preventing Exposure

HIV-infected individuals who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to it, but those with CD4 counts <150 cells/mm^3 should avoid activities known to be associated with increased risk **(BIII)**. These include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

Preventing Disease

When to Start Primary Prophylaxis

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV infection and who live in areas where histoplasmosis is highly endemic.[13] Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for patients with CD4 counts <150 cells/mm^3 who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**.

When to Stop Primary Prophylaxis

If used, primary prophylaxis can be discontinued in patients on potent ART once CD4 counts are ≥150 cells/mm^3 for 6 months **(BIII)**. Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm^3 **(BIII)**.

Treating Disease

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily), induced a more rapid and complete response, lowered mortality, and reduced toxicity.[14] Based on these findings, patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for at least 2 weeks or until they clinically improve **(AI)**. Another lipid formulation of amphotericin B can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B **(AIII)**. Step-down therapy to oral itraconazole, 200 mg 3 times daily for 3 days, and then 200 mg twice daily, should be given for a total of at least 12 months **(AII)**.[15] Because of potential drug interactions between itraconazole and both protease inhibitors and efavirenz, it is advisable to obtain serum levels of itraconazole after 2 weeks of therapy. A randomly obtained serum level of at least 1.0 µg/mL is recommended and levels >10 µg/mL are unnecessary.

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg 3 times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy **(AII)**.[15,16] The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption, but it is less well tolerated than the capsule formulation, which should be given with food.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4 count >300 cells/mm^3, should be managed in a manner similar to that used for a nonimmunocompromised host **(AIII)**.[15]

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg daily for 4 to 6 weeks **(AIII)**. This should be followed by maintenance therapy with itraconazole at a dose of 200 mg 2 or 3 times daily for at least 1 year and until resolution of abnormal CSF findings **(AIII)**.[15]

Oral posaconazole and voriconazole have been reported to be effective for histoplasmosis in a small number of patients who had AIDS or other immunosuppressive conditions[17-20] and may be reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**. Fluconazole is less effective

than itraconazole for histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily and may also be a reasonable alternative at this dose for those intolerant of itraconazole **(CII)**.[21] The echinocandins are not active against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII)**.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) is reportedly uncommon in HIV-infected patients with histoplasmosis.[22,23] ART should, therefore, **not** be withheld because of concern for the possible development of IRIS **(AIII)**.

All of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in antigen level suggests relapse. Because absorption of itraconazole can be erratic, a random serum itraconazole level should be obtained after 2 weeks of therapy if there is concern about adherence or if medications with potentially adverse interactions are added to the drug regimen. The serum concentration should be >1 µg/mL.

As previously indicated, IRIS is uncommon in HIV-infected individuals with histoplasmosis.[22,23]

Managing Treatment Failure

Mortality rates remain high for patients with AIDS who develop disseminated histoplasmosis, many of whom had never received ART before diagnosis with histoplasmosis.[3-5,12] Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy **(AIII)**. Oral posaconazole and voriconazole are reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**;[17-20] fluconazole also can be used at a dose of 800 mg daily **(CII)**.[21] Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir (Table 5). Posaconazole has fewer known drug interactions with ARV medications than voriconazole.

Preventing Recurrence

When to Start Secondary Prophylaxis

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated or CNS infection **(AIII)** and after re-induction therapy in those whose disease relapses despite initial receipt of appropriate therapy **(BIII)**. Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.[21,24] The role of voriconazole or posaconazole has not been evaluated.

When to Stop Secondary Prophylaxis

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients treated for histoplasmosis who have a good immunologic response to ART.[25] Subjects in that trial had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum antigen <2 units, and CD4 counts ≥150 cells/mm^3; and had been on effective ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months.[25] Thus, discontinuing suppressive azole antifungal therapy appears to be safe for patients who meet the previously described criteria, noting that the detectable antigen level is now designated as 2 ng/mL **(AI)**. Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII)**.

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[26,27] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of 400 mg/day or more through or beyond the first trimester of pregnancy.[28] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short term exposure to fluconazole.[29,30] Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, low dose for treatment of vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 1 of 2)

Preventing 1st Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**

Preferred Therapy:

- Itraconazole 200 mg PO once daily **(BI)**

Discontinue Primary Prophylaxis:

- If used, may discontinue if CD4 count ≥150 cells/mm^3 for 6 months on ART **(BIII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <150 cells/mm^3 **(BIII)**

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy

Preferred Therapy:

- Liposomal amphotericin B at 3 mg/kg IV daily **(AI)**

Alternative Therapy:

- Amphotericin B lipid complex or amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily **(AIII)**

Duration:

- For at least 2 weeks or until clinically improved

Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months **(AII)**, with dosage adjustment based on interactions with ARV (see Table 5) and itraconazole serum concentration

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID for ≥12 months **(AII)**, with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 2 of 2)

Alternative Therapy:

Note: These recommendations are based on limited clinical data (for patients intolerant to itraconazole who are only moderately ill).

- Posaconazole 400 mg PO BID **(BIII)**
- Voriconazole 400 mg PO BID for 1 day, then 200 mg PO BID **(BIII)**
- Fluconazole 800 mg PO daily **(CII)**

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks):

- Liposomal amphotericin B: 5 mg/kg IV daily **(AIII)**

Maintenance Therapy

- Itraconazole 200 mg PO BID (TID for at least 12 months and until resolution of abnormal CSF findings) with dosage adjustment based on interactions with ARV and itraconazole serum concentration **(AIII)**

Long-Term Suppressive Therapy (Secondary Prophylaxis)

Indications:

- For patients with severe disseminated or CNS infection after completion of at least 12 months of treatment **(AIII)**, *and*
- In patients who relapsed despite appropriate initial therapy **(BIII)**

Preferred Therapy:

- Itraconazole 200 mg PO daily **(AIII)**

Alternative Therapy:

- Fluconazole 400 mg PO daily **(BIII)**

*Criteria for Discontinuing Long Term Suppressive Therapy **(AI)**:*

- Received azole treatment for >1 year, *and*
- Negative fungal blood cultures, *and*
- Serum Histoplasma antigen <2 ng/mL, *and*
- CD4 count >150 cells/mm^3 for ≥6 months in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 count <150 cells/mm^3 **(BIII)**

Other Considerations:

- Itraconazole serum concentrations should be performed in all patients to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions **(AIII)**. Random serum concentrations (itraconazole + hydroxyitraconazole) should be >1 µg/mL.
- Itraconazole oral solution is preferred over capsule because of improved absorption, but is less well tolerated. However, this formulation may not be necessary if itraconazole concentration is increased by concomitant use of a CYP3A4 inhibitor such as ritonavir-boosted PIs.
- Acute pulmonary histoplasmosis in HIV-infected patients with CD4 count >300 cells/mm^3 should be managed the same as for non-immunocompromised patients **(AIII)**
- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; IV = intravenous; PI = protease inhibitor; PO = orally; TID = three times daily

References

1. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. Nov 1990;69(6):361-374. Available at http://www.ncbi.nlm.nih.gov/pubmed/2233233.
2. McKinsey DS, Spiegel RA, Hutwagner L, et al. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors, and pathophysiology. *Clin Infect Dis*. Jun 1997;24(6):1195-1203. Available at http://www.ncbi.nlm.nih.gov/pubmed/9195082.
3. Antinori S, Magni C, Nebuloni M, et al. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. *Medicine (Baltimore)*. Jan 2006;85(1):22-36. Available at http://www.ncbi.nlm.nih.gov/pubmed/16523050.
4. Baddley JW, Sankara IR, Rodriquez JM, Pappas PG, Many WJ, Jr. Histoplasmosis in HIV-infected patients in a southern regional medical center: poor prognosis in the era of highly active antiretroviral therapy. *Diagn Microbiol Infect Dis*. Oct 2008;62(2):151-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/18597967.
5. Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. *Clin Infect Dis*. Apr 15 2005;40(8):1199-1202. Available at http://www.ncbi.nlm.nih.gov/pubmed/15791523.
6. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. *Clin Infect Dis*. Mar 15 2005;40(6):844-852. Available at http://www.ncbi.nlm.nih.gov/pubmed/15736018.
7. Assi M, McKinsey DS, Driks MR, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. *Diagn Microbiol Infect Dis*. Jul 2006;55(3):195-201. Available at http://www.ncbi.nlm.nih.gov/pubmed/16545932.
8. Swartzentruber S, Rhodes L, Kurkjian K, et al. Diagnosis of acute pulmonary histoplasmosis by antigen detection. *Clin Infect Dis*. Dec 15 2009;49(12):1878-1882. Available at http://www.ncbi.nlm.nih.gov/pubmed/19911965.
9. Connolly PA, Durkin MM, Lemonte AM, Hackett EJ, Wheat LJ. Detection of histoplasma antigen by a quantitative enzyme immunoassay. *Clin Vaccine Immunol*. Dec 2007;14(12):1587-1591. Available at http://www.ncbi.nlm.nih.gov/pubmed/17913863.
10. Hage CA, Davis TE, Fuller D, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. *Chest*. Mar 2010;137(3):623-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/19837826.
11. Wheat LJ. Approach to the diagnosis of the endemic mycoses. *Clin Chest Med*. Jun 2009;30(2):379-389, viii. Available at http://www.ncbi.nlm.nih.gov/pubmed/19375642.
12. Tobon AM, Agudelo CA, Rosero DS, et al. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. *Am J Trop Med Hyg*. Sep 2005;73(3):576-582. Available at http://www.ncbi.nlm.nih.gov/pubmed/16172484.
13. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. May 1999;28(5):1049-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452633.
14. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. Jul 16 2002;137(2):105-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/12118965.
15. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. Oct 1 2007;45(7):807-825. Available at http://www.ncbi.nlm.nih.gov/pubmed/17806045.
16. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *Am J Med*. Apr 1995;98(4):336-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/7709945.
17. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. *Transplant infectious disease: an official journal of the Transplantation Society*. Sep-Dec 2005;7(3-4):109-115. Available at http://www.ncbi.nlm.nih.gov/pubmed/16390398.

18. Al-Agha OM, Mooty M, Salarieh A. A 43-year-old woman with acquired immunodeficiency syndrome and fever of undetermined origin. Disseminated histoplasmosis. *Archives of pathology & laboratory medicine*. Jan 2006;130(1):120-123. Available at http://www.ncbi.nlm.nih.gov/pubmed/16390228.

19. Restrepo A, Tobon A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. *J Infect*. Apr 2007;54(4):319-327. Available at http://www.ncbi.nlm.nih.gov/pubmed/16824608.

20. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. Apr 2009;53(4):1648-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/19139290.

21. Wheat J, MaWhinney S, Hafner R, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. *Am J Med*. Sep 1997;103(3):223-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/9316555.

22. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Apr 1 2005;40(7):1049-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/15825000.

23. Nacher M, Sarazin F, El Guedj M, et al. Increased incidence of disseminated histoplasmosis following highly active antiretroviral therapy initiation. *J Acquir Immune Defic Syndr*. Apr 1 2006;41(4):468-470. Available at http://www.ncbi.nlm.nih.gov/pubmed/16652055.

24. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. *J Acquir Immune Defic Syndr Hum Retrovirol*. Oct 1 1997;16(2):100-107. Available at http://www.ncbi.nlm.nih.gov/pubmed/9358104.

25. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Infect Dis*. May 15 2004;38(10):1485-1489. Available at http://www.ncbi.nlm.nih.gov/pubmed/15156489.

26. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.

27. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.

28. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.

29. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at http://www.ncbi.nlm.nih.gov/pubmed/18400803.

30. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at http://www.ncbi.nlm.nih.gov/pubmed/8987954.

Coccidioidomycosis (Last updated November 10, 2016; last reviewed June 14, 2017)

Epidemiology

Coccidioidomycosis is caused by a soil-dwelling fungus that consists of two species, *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in HIV-infected individuals have been reported in the areas in which the disease is highly endemic.[1] In the United States, these areas include the lower San Joaquin Valley and other arid regions in southern California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.[2] Recently, cases of coccidioidomycosis that appeared to be acquired in eastern Washington state have been reported.[3] Whether this is anomalous or is a manifestation of an expanding area of endemicity is not clear at this time. In some instances, coccidioidomycosis has been diagnosed in patients with HIV infection well outside the known endemic regions. These have presumably been the result of reactivation of a previously acquired infection.

The risk of developing symptomatic coccidioidomycosis after infection is increased in HIV-infected patients who have CD4 T lymphocyte (CD4) counts <250 cells/mm^3 or who have been diagnosed with AIDS.[4] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[5,6]

Clinical Manifestations

Lack of suppression of HIV replication and lower CD4 cell counts are associated with the severity of the presentation of coccidioidomycosis.[6] Four common syndromes of coccidioidomycosis have been described in HIV-infected patients: focal pneumonia, diffuse pneumonia, extrathoracic involvement including meningitis, and positive coccidioidal serology tests without evidence of localized infection.[7] In addition, patients with HIV infection may develop dissemination to other extrathoracic sites, including the bones and joints.

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. This diagnosis can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[8,9] However, coccidioidomycosis may present with hilar or mediastinal adenopathy, upper lobe infiltrates, night sweats, and peripheral blood eosinophilia, all of which are uncommon in bacterial pneumonia. The syndromes other than focal pneumonia usually occur in more immunosuppressed patients. Diffuse pulmonary disease presents with fever and dyspnea and can be difficult to clinically distinguish from *Pneumocystis* pneumonia.[10] Hypoxemia may be severe and serological tests are frequently negative at the time of presentation. Routine bacterial cultures from pulmonary secretions frequently reveal *Coccidioides* after an incubation time of less than one week. Meningitis presents with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile demonstrates low glucose levels with elevated protein and a lymphocytic pleocytosis. In addition, immunosuppressed patients with HIV infection may present with elevated coccidioidal serological titers without evidence of disease. A study in the era prior to potent ART described 13 patients, all with CD4 counts <350 cells/mm^3 and positive coccidioidal serologic tests. Five patients subsequently developed clinical illness at a median CD4 count of 10 cells/mm^3.[11]

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of spherules on histopathological examination of infected tissue. Blood cultures are positive in a minority of patients, usually those with diffuse pulmonary disease. Cultures of the CSF are positive in fewer than one-third of patients with coccidioidal meningitis. Unlike other endemic mycoses, *Coccidioides* grows relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a non-pigmented mould may be observed in as few as 3 days and can be confirmed as *Coccidioides* by gene probe. *Coccidioides* growing on an agar plate is a significant laboratory hazard because of the risk of inhalation of dislodged arthroconidia. Laboratory personnel should be alerted to the possibility of *Coccidioides* at the time the specimen is sent to the laboratory, and the plate lid securely taped.[12] Identification of the fungus should be

performed in biosafety level 3 (BSL 3) containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test associated with a compatable clinical syndrome. Patients with past coccidioidal infection without disease activity usually have negative serological tests. The nomenclature and variety of coccidioidal serological tests can be confusing.[13] The original assays examined two reactions. The first was the development of a precipitate in a tube when incubated with a heat-stable coccidioidal antigen preparation. This has been termed "tube precipitin" or TP response. It is due to an IgM antibody reaction, is not titratable, not useful in the diagnosis of meningitis, and is positive early in disease. If performed by immunodiffusion, it is termed IDTP. The second reaction originally detected the loss of serum complement activity in the presence of a heat-labile coccidioidal antigen preparation. This is called "complement-fixing" or CF, is due to an IgG response, is titratable, and its detection in the CSF is indicative of meningitis. CF antibody responses can also be measured by immunodiffusion (IDCF). In general, elevated CF titers suggest clinically active disease. Several companies offer enzyme immunoassays (EIAs). They appear to be similar to IDTP and IDCF with the following caveats. The IgM EIA has been associated with false positive results and the IgG EIA is not titratable. Both CF and EIA tests appear to be more sensitive than immunodiffusion assays. All coccidioidal serologic tests are positive less frequently in HIV infected patients with low CD4 cell counts than in those who are immunocompetent.[14] It is strongly recommended that clinical samples for serological testing be sent to laboratories with expertise in performing these assays.

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[15] serum[16] and other body fluids in samples from individuals with active coccidioidomycosis. It is most useful in diagnosing extrathoracic disseminated coccidioidomycosis. A recent study suggests that detection of coccidioidal antigen in the cerebrospinal fluid has a very high sensitivity and specificity for diagnosing coccidioidal meningitis.[17]

Preventing Exposure

HIV-infected individuals cannot completely avoid activities involving exposure to infection while living in or visiting areas where *Coccidioides* is endemic. They should, however, avoid extensive exposure to disturbed soil, such as at building excavation sites, and they should stay inside during dust storms **(BIII)**.

Preventing Disease

Primary antifungal prophylaxis (i.e. prophylaxis for individuals with negative serologic tests for *Coccidioides*) is of little benefit to patients with low CD4 cell counts who live in regions where *Coccidioides* is endemic[5] and it **is not recommended (AIII)**. Yearly or twice-yearly serological testing for coccidioidomycosis is reasonable for serologically negative HIV-infected individuals who live in regions endemic for coccidioidomycosis. Testing is also advised for individuals who have traveled to or lived in endemic areas in the past. Both IgM and IgG antibody testing using either an EIA or immunodiffusion technique are recommended. A new positive test suggests possible active disease in patients with low CD4 cell counts[11] and further clinical evaluation should be undertaken. If no signs, symptoms or laboratory abnormalities compatible with active coccidioidomycosis are identified, antifungal therapy with fluconazole 400 mg daily is recommended for those with CD4 counts <250 cells/mm^3 **(AIII)**. This should be continued until the CD4 count is ≥250 cells/mm^3 and ART has fully suppressed HIV replication **(BIII)**. Outside endemic regions, routine testing does not appear to be useful and **should not be performed (CIII)**.

Treating Disease

Initial therapy with a triazole antifungal agent given orally is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII)**. When prescribing triazoles, it should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage

adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with ritonavir- or cobicistat-containing regimens.

Without concomitant interacting drugs, fluconazole should be given as 400 mg daily **(AII)**, while itraconazole should be given in divided doses of 200 mg two to three times daily **(BII)**.[18,19] Itraconazole is preferred for those who have bone or joint disease **(AI)**.[20] Serum itraconazole levels should be measured after reaching steady state at 2 weeks to ensure adequate absorption. Data are limited for treatment with posaconazole[21,22] and voriconazole, but these agents are useful for patients who fail to respond to fluconazole or itraconazole **(BII)**. The dose of voriconazole is 200 mg twice daily after a loading dose of 400 mg twice daily for the first day **(AIII)**. Trough serum levels should be measured to ensure efficacy and avoid toxicity; a level of 1-5 mg/L is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used **(BII)**,[22] but the current extended-release tablet formulation is better tolerated by patients and provides more reliable absorption and serum levels. There is no established dosage with the tablet formulation for coccidioidomycosis but 300 mg daily is reasonable **(BIII)**. There are no published data on the use of the newly approved triazole antifungal isavuconazole for coccidioidomycosis in patients with HIV infection. Among nine patients with pulmonary disease without HIV infection, initial therapy with isavuconazole resulted in complete or partial success in 5 (56%).[23]

Patients with HIV infection and positive coccidioidal serologies but without clinical illness should be treated with antifungal therapy as previously described in the same manner as patients with focal pneumonia **(AII)**. For patients with CD4 cell counts <250/mm^3 who are not receiving suppressive antiretroviral therapy, fluconazole 400 mg daily should be given and continued until the CD4 cell count is ≥250/mm^3 and HIV RNA suppression has been achieved **(AIII)**. For those with CD4 cell counts already ≥250/mm^3 and on suppressive antiretroviral therapy, close clinical follow-up is recommended **(BIII)**.

Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or are severely ill with extrathoracic disseminated disease **(AII)**.[19] Most experience has been with the deoxycholate formulation, using an initial dose of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are no reported studies that have used lipid formulations of amphotericin B for the treatment of coccidioidomycosis, but these are likely to be as effective as the deoxycholate formulation and should be considered as an equivalent initial therapy, particularly if there is underlying renal dysfunction **(AIII)**. An initial daily dose of 3 to 5 mg/kg is appropriate.

Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII)**. Some specialists recommend combining amphotericin B with a triazole antifungal (fluconazole or itraconazole) 400 mg daily at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII)**.[19]

Treatment of patients with coccidioidal meningitis requires consultation with a specialist **(AIII)**. Therapy should begin with a triazole antifungal. IV or oral fluconazole at a dose of 400 to 800 mg daily is preferred **(AII)**,[24] but itraconazole also has been successfully used (BII).[25] Therapy with posaconazole **(CIII)**[22,26] or voriconazole **(BIII)**[27-29] has been described in individual cases. Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B is recommended **(AIII)**. If intrathecal therapy is required, it should be administered by someone very experienced in this technique.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Monitoring the CF antibody titer is useful in assessing response to therapy, and it should be measured every 12 weeks. A rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. As indicated previously, all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

The immune reconstitution inflammatory syndrome (IRIS) has been infrequently reported in HIV-infected persons with concomitant coccidioidomycosis.[30-32] Because of this, delaying initiation of potent antiretroviral therapy while treating coccidioidomycosis is not recommended **(AIII)**.

Managing Treatment Failure

Patients with severe coccidioidomycosis who fail treatment with fluconazole or itraconazole should have their treatment changed to IV amphotericin B, either deoxycholate or a lipid formulation **(AIII)**. For patients who are not severely ill, posaconazole **(BII)** and voriconazole **(BIII)** are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir or cobicistat-boosted regimens (see Table 5). Posaconazole has fewer known drug interactions with ARV medications than does voriconazole.

Therapy after Immune Reconstitution

Patients with peripheral blood CD4 lymphocyte counts ≥250/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[33] Moreover, a prospective study has demonstrated that the severity of coccidioidomycosis is less in those with lower HIV RNA and higher CD4 cell counts.[6] Given these facts, in HIV-infected patients with undetectable HIV RNA on potent ARV therapy who have a CD4 ≥250/mm^3, coccidioidomycosis should be managed no differently than it is in the general population **(AII)**.

For patients who meet the above criteria with focal pulmonary disease, treatment with triazole antifungal should continue for a minimum of 6 months **(AII)**. For patients with diffuse pulmonary disease and those with extrathoracic dissemination, antifungal therapy should continue for at least 12 months and usually much longer. Discontinuation of therapy should be based on clinical and immunological response in consultation with an expert. For patients with detectable HIV viremia or CD4 <250/mm^3, antifungal therapy at full dose should continue **(BIII)**.

Prevention of Relapse

Relapse occurs in 25% to 33% of HIV-uninfected patients who have diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis[34,35] and may occur in HIV-infected patients with CD4 counts ≥250 cells/mm^3 on potent ART[36]. Continued monitoring during coccidiomycosis therapy and after such therapy has been discontinued with clinical follow-up, serial chest radiographs and coccidioidal serology every 3 to 6 months should be performed. Because relapses have been reported in 80% of patients with meningitis in whom triazoles have been discontinued,[37] therapy for coccidioidal meningitis should be continued for life **(AII)**.

Special Considerations During Pregnancy

Women are generally at less risk than men for severe coccidioidomycosis and disease does not appear to worsen in women with prior coccidioidomycosis during pregnancy. However, coccidioidomycosis is likely to be severe and disseminated if infection is acquired during the second or third trimester of pregnancy.[38]

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[39] A recent systematic review and meta-analysis of cohort or case–control studies reporting fetal outcomes after exposure to any dose of fluconazole used in the first trimester of pregnancy found an increased risk of heart defects[40] but did not find an increase in the rate of overall malformations or in craniofacial defects. One registry-based cohort study (included in the systematic review)[41] and a more recent large population-based case-control study[42] specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

In addition in a nation-wide cohort study from Denmark oral fluconazole in pregnancy was associated with an increase risk of spontaneous abortion compared to unexposed women or those with topical azole exposure only.[42] Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short

term exposure. Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, 150 mg dose to treat vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[43,44] However, in general, all azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. One problematic area is coccidioidal meningitis, in which the only alternative treatment to triazole antifungals is IV or intrathecal amphotericin B. For such situations, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the mother, the infectious diseases consultant, and the obstetrician.[45] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies; for voriconazole, these occurred at doses lower than recommended for humans. There are no adequately controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII)**. Extensive clinical use of amphotericin B has not been associated with teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Recommendations for Treating Coccidiodomycosis (page 1 of 2)

Treating Mild Infections (Such As Focal Pneumonia or asymptomatic patients with positive serology and CD4 count <250 cells/mm^3)

Preferred Therapy:

- Fluconazole 400 mg PO once daily **(BII)***, *or*
- Itraconazole 200 mg PO twice daily **(BII)***

Alternative Therapy (For Patients Who Failed To Respond To Fluconazole Or Itraconazole):

- Voriconazole 200 mg PO twice daily after a loading dose of 400 mg twice on first day **(BIII)***; *or*
- Posaconazole (delayed release tablet) 300 mg PO daily after a loading dose of 300 mg twice daily for one day, then 300 mg once daily* **(BIII)*** *or*
- Posaconazole (oral suspension) 400 mg PO twice daily **(BII)***

Treating Bone or Joint Infections

Preferred Therapy:

- Itraconazole 200 mg PO twice daily **(AI)***

Alternative Therapy:

- Fluconazole 400 mg PO once daily **(BI)***

Treating Severe, Non-Meningeal Infection (Diffuse Pulmonary or Severely Ill Patients with Extrathoracic Disseminated Disease)—Acute Phase

Preferred Therapy:

- Lipid formulation amphotericin B 3–5 mg/kg IV daily **(AIII)**, *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)**
- Use until clinical improvement, then switch to triazole **(BIII)**

Alternative Therapy:

- Some specialists add a triazole (either fluconazole 400 mg daily or itraconazole 200 mg twice daily, with itraconazole preferred for bone or joint disease) to amphotericin B therapy and continue the triazole once amphotericin B is stopped **(BIII)**

Treatment For Meningeal Infections (Consultation With A Specialist Is Advised)

Preferred Therapy:

- Fluconazole 400–800 mg PO daily **(AII)**; IV if patient unable to take orally.

Recommendations for Treating Coccidiodomycosis (page 2 of 2)

Alternative Therapy:

- Itraconazole 200 mg PO twice to three-times daily* **(BII)**, *or*
- Voriconazole 200–400 mg PO twice daily after loading dose* **(BIII)**, *or*
- Posaconazole (delayed release tablet) loading dose of 300 mg twice daily on first day, then 300 mg once daily* **(CIII)**, *or*
- Posaconazole (oral suspension) 400 mg PO twice daily* **(CIII)**, *or*
- Intrathecal amphotericin B **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by a clinician experienced in this technique.

Duration of Therapy

*Focal Coccidioidal Pneumonia, or Asymptomatic Patients with Positive Serology and CD4 Count <250 cells/mm^3, Therapy Can Be Stopped If **(AII)**:*

- Clinically responded to ≥6 months of antifungal therapy (for patients with focal pneumonia), *and*
- CD4 count ≥250 cells/mm^3, and
- Receiving effective ART with virologic suppression, *and*
- Continued monitoring for recurrence should be performed using serial chest radiograph and coccidioidal serology every six to twelve months.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

- Relapse can occur in 25% to 33% of HIV-seronegative patients, and can occur in HIV patients with CD4 count >250 cells/mm^3
- Therapy is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts **(BIII)**.

Coccidioidal Meningitis:

- Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong **(AII)**

Other Considerations:

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.
- All triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

* It should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with efavirenz, ritonavir- or cobicistat-containing regimens.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; IgG = immunogloblulin G; IgM = immunoglobulin M; IV = intravenous; PO = orally

References

1. Jones JL, Fleming PL, Ciesielski CA, Hu DJ, Kaplan JE, Ward JW. Coccidioidomycosis among persons with AIDS in the United States. *J Infect Dis*. Apr 1995;171(4):961-966. Available at http://www.ncbi.nlm.nih.gov/pubmed/7706825.
2. Centers for Disease C, Prevention. Increase in Coccidioidomycosis - California, 2000-2007. *MMWR Morb Mortal Wkly Rep*. Feb 13 2009;58(5):105-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/19214158.
3. Litvintseva AP, Marsden-Haug N, Hurst S, et al. Valley fever: finding new places for an old disease: Coccidioides immitis found in Washington State soil associated with recent human infection. *Clin Infect Dis*. Jan 1 2015;60(1):e1-3. Available at http://www.ncbi.nlm.nih.gov/pubmed/25165087.
4. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. *Am J Med*. Mar 1993;94(3):235-240. Available at http://www.ncbi.nlm.nih.gov/pubmed/8095771.
5. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. *J Infect Dis*. Apr 2000;181(4):1428-1434. Available at

http://www.ncbi.nlm.nih.gov/pubmed/10753734.

6. Masannat FY, Ampel NM. Coccidioidomycosis in patients with HIV-1 infection in the era of potent antiretroviral therapy. *Clin Infect Dis*. Jan 1 2010;50(1):1-7. Available at http://www.ncbi.nlm.nih.gov/pubmed/19995218.
7. Fish DG, Ampel NM, Galgiani JN, et al. Coccidioidomycosis during human immunodeficiency virus infection. A review of 77 patients. Medicine (Baltimore). Nov 1990;69(6):384-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/2146461.
8. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis*. Jun 2006;12(6):958-962. Available at http://www.ncbi.nlm.nih.gov/pubmed/16707052.
9. Kim MM, Blair JE, Carey EJ, Wu Q, Smilack JD. Coccidioidal pneumonia, Phoenix, Arizona, USA, 2000-2004. *Emerg Infect Dis*. Mar 2009;15(3):397-401. Available at http://www.ncbi.nlm.nih.gov/pubmed/19239751.
10. Mahaffey KW, Hippenmeyer CL, Mandel R, Ampel NM. Unrecognized coccidioidomycosis complicating Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus and treated with corticosteroids. A report of two cases. *Arch Intern Med*. Jun 28 1993;153(12):1496-1498. Available at http://www.ncbi.nlm.nih.gov/pubmed/8512440.
11. Arguinchona HL, Ampel NM, Dols CL, Galgiani JN, Mohler MJ, Fish DG. Persistent coccidioidal seropositivity without clinical evidence of active coccidioidomycosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. May 1995;20(5):1281-1285. Available at http://www.ncbi.nlm.nih.gov/pubmed/7620011.
12. Stevens DA, Clemons KV, Levine HB, et al. Expert opinion: what to do when there is Coccidioides exposure in a laboratory. *Clin Infect Dis*. Sep 15 2009;49(6):919-923. Available at http://www.ncbi.nlm.nih.gov/pubmed/19663562.
13. Pappagianis D. Serologic studies in coccidioidomycosis. *Semin Respir Infect*. Dec 2001;16(4):242-250. Available at http://www.ncbi.nlm.nih.gov/pubmed/11740825.
14. Singh VR, Smith DK, Lawerence J, et al. Coccidioidomycosis in patients infected with human immunodeficiency virus: review of 91 cases at a single institution. *Clin Infect Dis*. Sep 1996;23(3):563-568. Available at http://www.ncbi.nlm.nih.gov/pubmed/8879781.
15. Durkin M, Connolly P, Kuberski T, et al. Diagnosis of coccidioidomycosis with use of the Coccidioides antigen enzyme immunoassay. *Clin Infect Dis*. Oct 15 2008;47(8):e69-73. Available at http://www.ncbi.nlm.nih.gov/pubmed/18781884.
16. Durkin M, Estok L, Hospenthal D, et al. Detection of Coccidioides antigenemia following dissociation of immune complexes. *Clin Vaccine Immunol*. Oct 2009;16(10):1453-1456. Available at http://www.ncbi.nlm.nih.gov/pubmed/19675225.
17. Kassis C, Zaidi S, Kuberski T, et al. Role of Coccidioides Antigen Testing in the Cerebrospinal Fluid for the Diagnosis of Coccidioidal Meningitis. *Clin Infect Dis*. Nov 15 2015;61(10):1521-1526. Available at http://www.ncbi.nlm.nih.gov/pubmed/26209683.
18. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. *Clin Infect Dis*. Apr 2000;30(4):658-661. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770727.
19. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis*. Nov 1 2005;41(9):1217-1223. Available at http://www.ncbi.nlm.nih.gov/pubmed/16206093.
20. Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med*. Nov 7 2000;133(9):676-686. Available at http://www.ncbi.nlm.nih.gov/pubmed/11074900.
21. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis*. Jun 15 2005;40(12):1770-1776. Available at http://www.ncbi.nlm.nih.gov/pubmed/15909265.
22. Stevens DA, Rendon A, Gaona-Flores V, et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest*. Sep 2007;132(3):952-958. Available at http://www.ncbi.nlm.nih.gov/pubmed/17573510.
23. Thompson GR, 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole Treatment of Cryptococcosis and Dimorphic Mycoses. *Clin Infect Dis*. Aug 1 2016;63(3):356-362. Available at http://www.ncbi.nlm.nih.gov/pubmed/27169478.
24. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med*. Jul 1 1993;119(1):28-35. Available at http://www.ncbi.nlm.nih.gov/pubmed/8498760.
25. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med*. Jan 15 1990;112(2):108-112. Available at http://www.ncbi.nlm.nih.gov/pubmed/2153012.

26. Schein R, Homans J, Larsen RA, Neely M. Posaconazole for chronic refractory coccidioidal meningitis. *Clin Infect Dis*. Dec 2011;53(12):1252-1254. Available at http://www.ncbi.nlm.nih.gov/pubmed/21987729.
27. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. *Clin Infect Dis*. Jun 15 2003;36(12):1619-1622. Available at http://www.ncbi.nlm.nih.gov/pubmed/12802765.
28. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of Coccidioides meningitis. *Antimicrob Agents Chemother*. Jun 2004;48(6):2341. Available at http://www.ncbi.nlm.nih.gov/pubmed/15155250.
29. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. Apr 2009;53(4):1648-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/19139290.
30. Mortimer RB, Libke R, Eghbalieh B, Bilello JF. Immune reconstitution inflammatory syndrome presenting as superior vena cava syndrome secondary to Coccidioides lymphadenopathy in an HIV-infected patient. *J Int Assoc Physicians AIDS Care (Chic)*. Nov-Dec 2008;7(6):283-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/18948432.
31. D'Avino A, Di Giambenedetto S, Fabbiani M, Farina S. Coccidioidomycosis of cervical lymph nodes in an HIV-infected patient with immunologic reconstitution on potent HAART: a rare observation in a nonendemic area. *Diagn Microbiol Infect Dis*. Feb 2012;72(2):185-187. Available at http://www.ncbi.nlm.nih.gov/pubmed/22104185.
32. Trible R, Edgerton N, Hayek S, Winkel D, Anderson AM. Antiretroviral therapy-associated coccidioidal meningitis. *Emerg Infect Dis*. Jan 2013;19(1):163-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/23260018.
33. Ampel NM. Delayed-type hypersensitivity, in vitro T-cell responsiveness and risk of active coccidioidomycosis among HIV-infected patients living in the coccidioidal endemic area. *Med Mycol*. Aug 1999;37(4):245-250. Available at http://www.ncbi.nlm.nih.gov/pubmed/10421859.
34. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NAIAD Mycoses Study Group. *Am J Med*. Sep 1990;89(3):282-290. Available at http://www.ncbi.nlm.nih.gov/pubmed/2168126.
35. Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. Mar 1995;98(3):249-256. Available at http://www.ncbi.nlm.nih.gov/pubmed/7872341.
36. Mathew G, Smedema M, Wheat LJ, Goldman M. Relapse of coccidioidomycosis despite immune reconstitution after fluconazole secondary prophylaxis in a patient with AIDS. *Mycoses*. Feb 2003;46(1-2):42-44. Available at http://www.ncbi.nlm.nih.gov/pubmed/12588482.
37. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? *Ann Intern Med*. Feb 1 1996;124(3):305-310. Available at http://www.ncbi.nlm.nih.gov/pubmed/8554225.
38. Peterson CM, Schuppert K, Kelly PC, Pappagianis D. Coccidioidomycosis and pregnancy. *Obstet Gynecol Surv*. Mar 1993;48(3):149-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/8441516.
39. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.
40. Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: A systematic review and meta-analysis. *Reprod Toxicol*. Apr 2015;52:78-82. Available at http://www.ncbi.nlm.nih.gov/pubmed/25724389.
41. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. Aug 29 2013;369(9):830-839. Available at http://www.ncbi.nlm.nih.gov/pubmed/23984730.
42. Howley MM, Carter TC, Browne ML, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. May 2016;214(5):657 e651-659. Available at http://www.ncbi.nlm.nih.gov/pubmed/26640069.
43. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.
44. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.
45. Bercovitch RS, Catanzaro A, Schwartz BS, Pappagianis D, Watts DH, Ampel NM. Coccidioidomycosis during pregnancy: a review and recommendations for management. *Clin Infect Dis*. Aug 2011;53(4):363-368. Available at http://www.ncbi.nlm.nih.gov/pubmed/21810749.

Cytomegalovirus Disease (Last updated November 4, 2015; last reviewed November 4, 2015)

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes virus family that can cause disseminated or localized end-organ disease in HIV-infected patients with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV (seropositive) and therefore represents either re-activation of latent infection or re-infection with a novel strain.

End-organ disease caused by CMV occurs in patients with advanced immunosuppression, typically those with CD4 T lymphocyte cell (CD4) counts <50 cells/mm^3, who are either not receiving or have failed to respond to antiretroviral therapy (ART).[1-3] Other risk factors include previous opportunistic infections (OIs), a high level of CMV viremia (most often measured by polymerase chain reaction [PCR]), and high plasma HIV RNA levels (>100,000 copies/mL).

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis sometime between the diagnosis of AIDS and death.[1-3] The incidence of new cases of CMV end-organ disease has declined by ≥95% with the advent of ART.[4,5] For those with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the pre-ART era. However, even for those with immune recovery sufficient to discontinue anti-CMV therapy, that is, CD4+ counts >100 cells/mm^3, relapse of the retinitis occurs at a rate of 0.03/person-year and occasionally can occur at CD4 counts as high as 1,250 cells/mm^3.[6] Therefore, whether anti-CMV therapy is continued or not, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately is bilateral in most patients in the absence of therapy or immune recovery.[6] In patients with unilateral CMV retinitis and CD4 count <50 cells/mm^3, rates of contralateral disease approach those of the pre-ART era.[6]

Peripheral retinitis may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula or optic nerve are associated with decreased visual acuity or central field defects. CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage, with little inflammation of the vitreous unless immune recovery with ART intervenes.[1] Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have a more granular appearance.

In the absence of ART or specific anti-CMV therapy, retinitis invariably progresses, usually within 10 to 21 days after presentation. Progression of retinitis occurs in fits and starts and causes a characteristic brushfire pattern, with a granular, white leading edge advancing before an atrophic gliotic scar.[7]

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.[2] The most frequent clinical manifestations are weight loss, anorexia, abdominal pain, debilitating diarrhea, and malaise. In the colon, and especially in the cecum, CMV can produce perforation and present as an acute abdomen. If CMV colitis is present, computed tomography may show colonic thickening. Hemorrhage and perforation can be life-threatening complications.

Esophagitis occurs in a small percentage of patients with AIDS who experience CMV end-organ disease and causes odynophagia, nausea, and occasionally midepigastric or retrosternal discomfort. Colitis and esophagitis may cause fever.

CMV pneumonitis is extremely uncommon. CMV is detected frequently in the bronchoalveolar lavage but is a bystander most of the time and should trigger a search for a more likely causative agent.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.[8] Patients with dementia caused by CMV encephalitis typically have lethargy, confusion, and fever. Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels, and normal-to-elevated protein levels. Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement of computed tomography or magnetic resonance images is highly suggestive of CMV ventriculoencephalitis rather than HIV-related neurologic disease. CMV polyradiculomyelopathy causes a Guillian-Barre–like syndrome characterized by urinary retention and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported and sacral paresthesia can occur. The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100–200 neutrophils/μL and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

CMV viremia can be detected by PCR, antigen assays, or culture and is usually, but not invariably, present in end-organ disease. Viremia as detected by one of these assays can be present in disease-free patients with low CD4 cell counts—that is, in the absence of end-organ disease.[8-13] Blood tests to detect CMV by antigen detection, culture, or PCR are not recommended for diagnosis of CMV end-organ disease because of their poor positive predictive value. A negative serum or plasma PCR assay also does not rule out CMV end-organ disease.

Of note, patients with CMV retinitis have CMV DNA detected in the vitreous in around 80% of cases, but in only 70% in the blood, with the remaining cases diagnosed by clinical criteria plus response to therapy.[14,15] CMV PCR can be particularly useful in assessing CSF or vitreous or aqueous humor specimens; a positive result is highly suggestive that CMV is the cause of end-organ disease. However, PCR assays are not standardized; therefore, sensitivity, specificity, and interassay comparability are not clearly delineated.

Presence of serum antibodies to CMV is not diagnostically useful, although a negative immunoglobulin G antibody level indicates that CMV is unlikely to be the cause of the disease process.

CMV retinitis usually is diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis in that setting has a 95% positive predictive value. In rare cases, diagnosis may be difficult and PCR of aqueous or vitreous specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and toxoplasmosis—can be useful for establishing the diagnosis.

CMV colitis is usually diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions.[2,16] CMV esophagitis is diagnosed by presence of ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.[2] Specimens may contain many inclusion bodies or rare, isolated inclusion bodies. The significance of such inclusion bodies is determined by clinical judgment plus the presence or absence of other plausible etiologies.

Culturing CMV from a biopsy or cells brushed from the colon or the esophagus is insufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes because a substantial number of patients with low CD4 cell counts may have positive cultures in the absence of clinical disease.[13]

The diagnosis of CMV pneumonitis is difficult and requires consistent clinical and radiological findings (i.e., diffuse pulmonary interstitial infiltrates, fever, and cough or dyspnea), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis.[11]

CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and the presence of CMV in CSF or brain tissue, most often evaluated with PCR.[3,9,12]

Preventing Exposure

HIV-infected patients who belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive may be tested for antibody to CMV **(BIII)**. That includes individuals who have not had contact with men who have sex with men or used injection drugs, and patients without extensive exposure to children in day care centers. HIV-infected adolescents and adults should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk of exposure to CMV as well as other sexually transmitted pathogens **(AII)**.

HIV-infected adults and adolescents who are CMV-seronegative and provide child care (or are parents of children in day care facilities) should be informed that they are at increased risk of acquiring CMV infection **(BI)**. Risk of acquiring CMV infection can be diminished with optimal hygienic practices, such as handwashing and use of latex gloves **(AIII)**. HIV-infected adolescents, and adults who are seronegative for CMV and who require blood transfusion should be given only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations **(BIII)**.

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/mm^3. Before ART was widely available, daily use of oral ganciclovir (no longer marketed in the United States) for primary prophylaxis significantly reduced incidence of CMV disease in a randomized, placebo-controlled trial.[17] However, such prophylactic therapy never became standard of care because of the cost, toxicity, and number-needed-to-treat to reduce disease. More recently, another randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) might reduce CMV end-organ disease in AIDS patients at high risk (CD4 count <100 cells/mm^3 and CMV viremia detected by plasma CMV DNA PCR assay) in the era of modern ART.[18] This study failed to show a benefit for such preventive therapy; therefore, valganciclovir primary prophylaxis **is not recommended** either in patients who will be receiving ART, or in patients who will not be receiving ART **(AI)**.

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients should be made aware of the implications of increased floaters in the eye and should be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint **(BIII)**. In the pre-modern ART era, some specialists recommended ophthalmologic examinations every 3 ro 4 months for patients with CD4 cells <50 cells/mm^3, as up to one-half of early CMV retinitis was asymptomatic **(CIII)**. However, with the decline in CMV incidence in the modern ART era, the value of this recommendation is unknown.

Treating Disease

CMV retinitis should ideally be treated with the active participation of an opthalmologist who is familiar with the diagnosis and management of retinal disease.

Oral valganciclovir **(AI)**, intravenous (IV) ganciclovir **(AI)**, IV ganciclovir followed by oral valganciclovir **(AI)**, IV foscarnet **(AI)**, and IV cidofovir **(BI)** are all effective treatments for CMV retinitis.[7,19-26] The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approxiamately 6 months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis **(AIII)**. The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications

and ability to adhere to treatment **(AIII)**. Systemic therapy has been documented to reduce CMV involvement of the contralateral eye,[19] to reduce CMV visceral disease, and to improve survival.[20,27] Prevention of contralateral eye involvement, visceral disease, and the benefits on survival should be considered when choosing among oral, IV, and local options. Given the evident benefits of systemic treatment, when medically and logistically feasible, treatment regimens for CMV retinitis should include a systemic component. There have been few comparative trials comparing regimen efficacy during the past 15 years. None of the listed regimens has been proven, in a clinical trial, to have superior efficacy related to protecting vision. Thus, clinical judgment must be used when choosing a regimen.[21-25] Early clinical trials were conducted with oral ganciclovir, a preparation with poor bioavailability that is no longer marketed in the United States. In these guidelines, valganciclovir has replaced oral ganciclovir in recommendations even though the best data in some situations come from early trials with oral ganciclovir.

In studies conducted in the pre-ART era,[23] ganciclovir intraocular implant (no longer available) plus oral ganciclovir was superior to once-daily IV ganciclovir for treatment of CMV retinitis. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, HIV specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions (within 1500 microns of the fovea) **(AIII)**. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications.[19] For patients with small peripheral lesions, oral valganciclovir alone often is adequate **(AI)**.

Because ART can control CMV retinitis without anti-CMV therapy in patients who develop substantial immune recovery, some clinicians may consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naive patients who are initiating ART. However, this strategy has multiple potential drawbacks: ART can take 3 to 6 months to fully control HIV replication and stimulate sufficient immune recovery to control the retinitis. Ocular complications, such as immune recovery uveitis (IRU) and retinal detachment are related to lesion size, so minimizing lesion size with anti-CMV therapy until there is sufficient immune recovery to control the retinitis is logical. Furthermore, evidence from both the pre-ART and ART eras demonstrate that specific anti-CMV therapy decreases mortality among patients with CMV retinitis and immune compromise.[13,20,26,28] In addition data from the ART era demonstrate that the use of systemic therapy for patients with CMV retinitis is associated with decreased retinitis progression, contralateral eye involvement, and visceral disease, as well as a reduction in mortality.[27] Moreover, some reports in the current era indicate that only 50% of some patient populations with CMV retinitis will experience immune recovery sufficient to meet criteria for discontinuation of anti-CMV therapy.[29] Therefore, even in ART-naive patients with small peripheral lesions, treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery will be beneficial **(AII)**. Systemic therapy is given twice daily for the first 14 to 21 days (induction) followed by once daily dosing (maintenance) until immune reconstitution occurs (see When to Stop Maintenance Therapy below).

For patients who have colitis or esophagitis, many HIV specialists recommend anti-CMV therapy for 21 to 42 days **(CII)** or until signs and symptoms have resolved. Some HIV specialists would withhold therapy for mild disease if ART is to be initiated soon or can be optimized **(CIII)**. IV ganciclovir generally is the therapy of choice, therapy can be switched to oral valganciclovir once the patient can tolerate oral medications **(BI)**; foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment limiting or in unusual cases of ganciclovir-resistant virus **(BIII)**. Oral valganciclovir can be used in patients with mild disease **(BIII)**.

Experience treating well-documented CMV pneumonia in patients with HIV infection is limited and anecdotal. Treatment with IV ganciclovir, or alternatively, with foscarnet, is logical **(CIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Therapy for well-documented neurologic disease also has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, some experts would initiate therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach

(CIII). Optimizing ART is important, as in all types of CMV disease **(BIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Special Considerations with Regard to Starting Antiretroviral Therapy

Visual impairment caused by complications of immune reconstitution inflammatory syndrome (IRIS), such as macular edema, may occur in patients who have active CMV retinitis and those who have had CMV retinitis in the recent or distant past. One historical controlled study suggested a substantial increase in immune reconstitution uveitis (IRU, described below) in association with immediate as opposed to deferred initiation of ART (71% vs. 31%),[30] suggesting that a delay in therapy until retinitis was controlled might be beneficial in reducing the likelihood or severity of IRU. However, this strategy must be weighed against the potential for occurrence of other OIs if ART initiation is delayed.

CMV replication usually is controlled within 1 to 2 weeks after anti-CMV therapy is initiated, and in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.04 per person-year).[29] Most experts would not delay ART for more than 2 weeks after starting anti-CMV therapy for retinitis or for other end-organ diseases caused by CMV **(CIII)**. IRIS is a particular concern with any neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, most experts would not defer initiation of ART for more than 2 weeks, although clinical judgment based on individual cases is needed **(CIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Indirect ophthalmoscopy through a dilated pupil should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment. The purpose of such examinations is to evaluate efficacy of treatment and to detect complications such as retinal detachment. Monthly fundus photographs, using a standardized technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that relapses and other retinal complications still occasionally occur in patients with immune reconstitution.

Adverse effects of ganciclovir/valganciclovir include anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Ganciclovir-related neutropenia often can be reversed with hematopoietic growth factors.[31,32] Adverse effects of foscarnet include nephrotoxicity, and electrolyte abnormalities; seizures occur, characteristically in the context of renal insufficiency, and anemia.

In patients receiving ganciclovir or foscarnet, complete blood counts, serum electrolytes (including potassium, magnesium, calcium, and phosphorus), and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy **(AIII)**. Cidofovir is associated with dose-related nephrotoxicity, neutropenia, uveitis, and hypotony. In patients receiving IV cidofovir, blood urea nitrogen and creatinine levels should be tested and urinalysis performed before each infusion; drug administration is contraindicated if renal dysfunction or significant proteinuria is detected. IV cidofovir requires prehydration and oral probenecid before administration. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony even when organ dysfunction does not appear to include retinitis. Intraocular injections can be associated with bacterial or fungal infections, hemorrhage, or retinal detachment.

As noted previously, patients with CMV retinitis must have careful ophthalmologic monitoring to detect and manage the wide range of complications related to CMV, the drugs used to treat CMV, and IRIS. IRU, an ocular form of IRIS presumed to be an adverse immunologic reaction to CMV, is characterized by inflammation in the anterior chamber or vitreous in the setting of immune recovery after initiation of ART. IRU usually is observed in patients with a substantial rise in CD4 cell count in the first 4 to 12 weeks after initiation of ART.[33-37] The estimated incidence of IRU is 0.02/person-year after immune recovery.[38] Ocular complications of IRU include macular edema and development of epiretinal membranes, which can cause loss of vision.

Treatment of IRU usually consists of some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.[33,39] Many experts would use both corticosteroids and anti-CMV therapy **(CIII)**. Data are insufficient on which to base a recommendation regarding the preferred route of corticosteroid administration; periocular, intravitreal, and oral administration all have been reported to be potentially successful. When oral corticosteroids are used, a short course rather than chronic therapy usually is recommended **(BIII)**.[40] IRU can occur even months or years after successful treatment of CMV retinitis in patients with a history of CMV retinitis who subsequently start taking ART or have such therapy optimized.

Early after the initiation of ART, patients remain at risk for development of CMV retinitis.[41] Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similarly to any patient with CMV retinitis, and continuing the same ART regimen **(AI)**. Corticosteroids are not recommended **(AIII)**. In addition, in the absence of uveitis, corticosteroids should not be used in patients undergoing treatment for CMV retinitis who have worsening of retinitis upon ART initiation. In this situation, anti-CMV therapy and ART regimens should be continued **(AIII)**.

Managing Treatment Failure

Failure of therapy for CMV retinitis or relapse is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.42 Treatment failure also may be a result of inadequate anti-CMV drug levels in the eye or CMV drug resistance. Many experts believe that early relapse is most often caused by the limited intraocular penetration of systemically administered drugs.[39,43,44]

When relapse occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction with the same drug as used for maintenance followed by re-institution of maintenance therapy, although results are likely to be seen for progressively shorter periods with each relapse **(BIII)**.[45] Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis **(CIII)**.[45] That drug combination, however, is associated with substantial toxicity.

Drug resistance occurs in patients receiving long-term anti-CMV therapy.[46-49] Rates of approximately 25% per person-year were reported in the pre-ART era[46,50,51] and reported rates are similar for ganciclovir, foscarnet, and cidofovir.[46,47] In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).[52] Low-level resistance to ganciclovir occurs through mutations in the CMV UL97 (phosphotransferase) gene, and high-level resistance to ganciclovir typically occurs because of mutations in both the CMV UL97 and UL54 (DNA polymerase) genes.[48,53-57] Resistance to foscarnet or cidofovir occurs because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir often is associated with cross resistance to cidofovir[55] and occasionally to foscarnet.[56] Although early relapse typically is not a result of resistance, later relapse may be. Because patients with resistant CMV are most likely to have mutations in the CMV UL97 gene, and because a limited number of mutations are responsible for most drug resistance, susceptibility testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay[58,59] may be reasonable for patients who relapse on therapy.[60] Virus in the eye and in the blood are identical in more than 90% of cases;14 evaluating the blood for resistance is reasonable, and detection of resistance in the blood or urine correlates with clinical behavior of the retinitis in most, but not all, cases.[61]

Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours, correlates well with conventional drug susceptibility testing and clinical outcomes,[60] and therefore has clinical utility for patients in whom therapy has failed. Conventional methods of culture and susceptibility testing and viral sequencing often are not available in clinical laboratories because they are too time-consuming or costly. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure. UL97 mutants usually respond to foscarnet, as do some UL54 mutants. Patients with high-level ganciclovir-resistant isolates will require a switch to alternative therapy.[62] Many clinicians will treat with a series of intravitreal injections of foscarnet and/or systemic foscarnet **(CIII)**.

Preventing Recurrence

When to Start Maintenance Therapy

With regard to CMV retinitis, after induction therapy, chronic maintenance therapy should be continued,[8,12,19,22,63] until immune reconstitution occurs as a result of ART **(AI)**. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Intravitreal therapy alone will not protect against contralateral or extraocular disease, however: oral or intravenous therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred. Repetitive intravitreous injections of fomivirsen also have been demonstrated to be effective in randomized clinical trials, but that drug, is no longer available in the United States.

The choice of regimen (i.e., which drug(s) and whether given intravitreally, orally or IV) should be made in consultation with an ophthalmologist, and considerations should include the anatomic location of the retinal lesion, vision in the contralateral eye, and a patient's immunologic and virologic status and response to ART.

Repetitive intravitreous injections of ganciclovir or of foscarnet have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series. Because of the risk of hypotony and uveitis, and the substantially increased risk of immune recovery uveitis with intravitreal cidofovir, intravitreal administration of cidofovir should be reserved for extraordinary cases.[64]

CMV retinitis requires a chronic regimen until an increase in CD4 cell count to >100 cells/mm^3 in response to ART has been sustained for 3 to 6 months **(AI)**.[65]

After resolution of the acute CMV syndrome, and after initiation of effective ART, chronic maintenance therapy is not routinely recommended for CMV gastrointestinal disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis or relapses have occurred **(BII)**.

When To Stop Maintenance Therapy

Maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose lesions have been treated for at least 3 to 6 months and are inactive and who have had sustained (i.e., 3–6 months) increases in CD4 cell counts to >100 cells/mm^3 in response to ART **(AII)**.[4,66-72] Such decisions should be made in consultation with an ophthalmologist. A 3% relapse rate is reported in patients whose anti-CMV therapy has been discontinued for immune recovery, and no level of CD4 cell count is absolutely safe (relapses have been reported at CD4 cell counts of 1250 cells/mm^3). Therefore, in all patients for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and for IRU should be performed at least every 3 months and periodically after immune reconstitution **(AIII)**. Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis, and therefore is not recommended **(BII)**.

Relapse of CMV retinitis occurs frequently in patients whose anti-CMV maintenance therapies have been discontinued and whose CD4 counts have decreased to <50 cells/mm^3.[73] Therefore, reinstitution of maintenance therapy should occur when the CD4 count has decreased to <100 cells/mm^3 **(AIII)**.

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for non-pregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant HIV-infected adults **(AIII)**. For retinal disease, use of intravitreous injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs **(BIII)**. Systemic antiviral therapy as discussed should then be started after the first trimester.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.[74-76] Safe use in human pregnancy after organ

transplantation has been reported,[74,75] and use in late pregnancy to treat fetal CMV infection in non-HIV-infected women has also been reported.[77]

Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome.[78] Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended **(AIII)**.

On the basis of limited data, toxicity reports and studies, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy **(BIII)**. No experience has been reported with the use of valganciclovir in human pregnancy, but concerns are expected to be the same as with ganciclovir. The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. No data exist to support use of pooled or CMV-specific intravenous immunoglobulin in this clinical situation.

Primary infection, reactivation and reinfection with different CMV strains during pregnancy[79] can all lead to in utero transmission and congenital CMV. Although about one-third of newborns acquire congenital CMV infection after primary infection, only approximately 1% to 2% of newborns acquire CMV after a recurrent infection in HIV-uninfected women. Because >90% of HIV-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is expected to be low.[80-84] However, recent studies of HIV-exposed infants suggest that rates of congenital CMV may be increased, ranging from 2% to 7%,[85,86] with higher rates in babies born to mothers with CD4 <200 cells/mm^3 and in HIV-infected infants. Maternal ART in pregnancy has been associated with decreased rates of perinatal/early postnatal CMV and occurrence of related clinical symptoms among HIV-infected and HIV-exposed infants.[87]

Up to 90% of infants who are symptomatic at birth will have serious long-term problems, including hearing loss, visual impairment, mental retardation and/or cognitive impairment, but only 5% to 15% of asymptomatic newborns are at risk for serious long-term impairment. However, asymptomatic congenital CMV infection is associated with late-onset hearing loss in non-HIV-infected children.[88] In women with CMV disease in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation, although from studies in HIV-uninfected populations, only about 5% to 25% of infected newborns have ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel). Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. Although invasive fetal testing was associated with increased rates of perinatal HIV transmission in early studies,[89] more recent data suggests that risk may be minimal in women on effective ART and with undetectable HIV-RNA levels.[89-91] Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

If fetal CMV infection is confirmed, there is no standard therapy for *in utero* treatment. A non-randomized trial of CMV hyperimmune globulin suggested potential benefit of passive immunotherapyfor treatment of acute fetal CMV infection, with decreased incidence of having a symptomatic newborn at birth[92] and regression of fetal cerebral abnormalities.[93] However, a well-designed, prospective, randomized, placebo-controlled study with relatively large sample size subsequently found no benefit of CMV hyperimmune globulin in pregnant women.94 A larger placebo-controlled trial of CMV hyperimmune globulin currently is underway at NICHD Maternal Fetal Units across the United States [ClinicalTrials.gov Identifier NCT01376778].

Routine screening for CMV infection in pregnancy is not recommended in the absence of effective *in utero* therapy. Treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated **(AIII)**.

Recommendations for Treating Cytomegalovirus Infections (page 1 of 2)

Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4 count >100 cells/mm^3.

Managing CMV Retinitis

- The choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), the level of immunosuppression, and other factors (e.g., concomitant medications, ability to adhere to treatment) **(AIII)**.
- Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reduce CMV visceral disease and improve survival,whenever feasible, treatment should include systemic therapy.
- The ganciclovir ocular implant, which is effective for treatment of CMV retinitis, is no longer available.

Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight Threatening Lesions (within 1500 microns of the fovea)

Preferred Therapy:

- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) for 1–4 doses over a period of 7–10 days to provide higher intraocular levels of drug and faster control of the infection until steady state intraocular ganciclovir concentrations are achieved **(AIII)**; *plus*
- Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily **(AI)**

Alternative Therapy

- Intravitreal injections as listed above **(AIII)**; *plus* one of the following systemic therapy:
  - Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily **(AI)**, *or*
  - Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily **(AI)**, *or*
  - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **(AI)**, *or*
  - Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) **(BI)**.

  Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid

For Peripheral Lesions

- Administer one of the systemic antiviral therapy listed above for the first 3–6 months until ART induced immune recovery **(AII)**.

IRU:

- Minimizing lesion size by treating all CMV retinitis lesions until there is immune recovery may reduce the incidence of IRU **(BII)**.
- IRU might develop in the setting of immune reconstitution.

Treatment of IRU:

- Periocular corticosteroid or a short course of systemic steroid (BIII).

Stopping Chronic Maintenance Therapy for CMV Retinitis:

- CMV treatment for at least 3–6 months, **and** lesions are inactive, **and** with CD4 count >100 cells/mm^3 for 3 to 6 months in response to ART **(AII)**.
- Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution **(AIII)**.

Reinstituting Chronic Maintenance for CMV Retinitis:

- CD4 count <100 cells/mm^3 **(AIII)**.

Recommendations for Treating Cytomegalovirus Infections (page 2 of 2)

Managing CMV Esophagitis or Colitis

- Doses are the same as for CMV retinitis.

Preferred Therapy:

- Ganciclovir 5 mg/kg IV q12h, may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy **(BI)**.

Alternative Therapy:

- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h **(BIII)**—for patients with treatment limiting toxicities to ganciclovir or with ganciclovir resistance; *or*
- Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption **(BIII)**; *or*
- For mild cases: If ART can be initiated or optimized without delay, withholding CMV therapy may be considered **(CIII)**.

Duration of Anti-CMV Therapy:

- 21–42 days or until signs and symptoms have resolved **(CII)**.

Note: Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)**

Managing Well-Documented CMV Pneumonitis:

- Doses are the same as for CMV retinitis.
- Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable **(CIII)**.
- The role of oral valganciclovir has not been established.
- The optimal duration of therapy has not been established.

Managing CMV Neurological Disease

- Doses are the same as for CMV retinitis.
- **Treatment should be initiated promptly.**
- Combination of ganciclovir IV plus foscarnet IV to stabilize disease and maximize response **(CIII)**.
- Optimal duration of therapy has not been established.
- The role of oral valganciclovir has not been established.
- Optimize ART to achieve viral suppression and immune reconstitution **(BIII)**.

Key to Acronyms: ART = antiretroviral therapy; BID = twice a day; CMV = Cytomegalovirus; IRU = immune recovery uveitis; PO = orally; IV = intraveneously; q(n)h = every "n" hours

References

1. Jabs DA, Van Natta ML, Kempen JH, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol*. Jan 2002;133(1):48-61. Available at http://www.ncbi.nlm.nih.gov/pubmed/11755839.
2. Dieterich DT, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr*. 1991;4 Suppl 1:S29-35. Available at http://www.ncbi.nlm.nih.gov/pubmed/1848619.
3. Arribas JR, Storch GA, Clifford DB, Tselis AC. Cytomegalovirus encephalitis. *Ann Intern Med*. Oct 1 1996;125(7):577-587. Available at http://www.ncbi.nlm.nih.gov/pubmed/8815757.
4. Jabs DA, Van Natta ML, Holbrook JT, et al. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. *Ophthalmology*. Apr 2007;114(4):780-786. Available at http://www.ncbi.nlm.nih.gov/pubmed/17258320.
5. Schwarcz L, Chen MJ, Vittinghoff E, Hsu L, Schwarcz S. Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. *AIDS*. Feb 20 2013;27(4):597-605. Available at http://www.ncbi.nlm.nih.gov/pubmed/23079812.
6. Jabs DA, Van Natta ML, Thorne JE, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology*. Dec 2004;111(12):2232-2239. Available at http://www.ncbi.nlm.nih.gov/pubmed/15582079.

7. Holland GN. AIDS and ophthalmology: the first quarter century. *Am J Ophthalmol*. Mar 2008;145(3):397-408. Available at http://www.ncbi.nlm.nih.gov/pubmed/18282490.

8. Arribas JR, Clifford DB, Fichtenbaum CJ, Commins DL, Powderly WG, Storch GA. Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. *J Infect Dis*. Aug 1995;172(2):527-531. Available at http://www.ncbi.nlm.nih.gov/pubmed/7622897.

9. Dodt KK, Jacobsen PH, Hofmann B, et al. Development of cytomegalovirus (CMV) disease may be predicted in HIV-infected patients by CMV polymerase chain reaction and the antigenemia test. *AIDS*. Mar 1997;11(3):F21-28. Available at http://www.ncbi.nlm.nih.gov/pubmed/9147416.

10. Zurlo JJ, O'Neill D, Polis MA, et al. Lack of clinical utility of cytomegalovirus blood and urine cultures in patients with HIV infection. *Ann Intern Med*. Jan 1 1993;118(1):12-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/8093214.

11. Rodriguez-Barradas MC, Stool E, Musher DM, et al. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. *Clin Infect Dis*. Jul 1996;23(1):76-81. Available at http://www.ncbi.nlm.nih.gov/pubmed/8816133.

12. Wolf DG, Spector SA. Diagnosis of human cytomegalovirus central nervous system disease in AIDS patients by DNA amplification from cerebrospinal fluid. *J Infect Dis*. Dec 1992;166(6):1412-1415. Available at http://www.ncbi.nlm.nih.gov/pubmed/1331254.

13. Deayton JR, Prof Sabin CA, Johnson MA, Emery VC, Wilson P, Griffiths PD. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. *Lancet*. Jun 26 2004;363(9427):2116-2121. Available at http://www.ncbi.nlm.nih.gov/pubmed/15220032.

14. Hu H, Jabs DA, Forman MS, et al. Comparison of cytomegalovirus (CMV) UL97 gene sequences in the blood and vitreous of patients with acquired immunodeficiency syndrome and CMV retinitis. *J Infect Dis*. Apr 1 2002;185(7):861-867. Available at http://www.ncbi.nlm.nih.gov/pubmed/11920309.

15. Jabs DA, Martin BK, Forman MS, Ricks MO, Cytomegalovirus R, Viral Resistance Research G. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression, and occurrence of resistant CMV in patients with CMV retinitis. *J Infect Dis*. Aug 15 2005;192(4):640-649. Available at http://www.ncbi.nlm.nih.gov/pubmed/16028133.

16. Laine L, Bonacini M, Sattler F, Young T, Sherrod A. Cytomegalovirus and Candida esophagitis in patients with AIDS. *J Acquir Immune Defic Syndr*. 1992;5(6):605-609. Available at http://www.ncbi.nlm.nih.gov/pubmed/1316961.

17. Spector SA, McKinley GF, Lalezari JP, et al. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. Roche Cooperative Oral Ganciclovir Study Group. *N Engl J Med*. Jun 6 1996;334(23):1491-1497. Available at http://www.ncbi.nlm.nih.gov/pubmed/8618603.

18. Wohl DA, Kendall MA, Andersen J, et al. Low rate of CMV end-organ disease in HIV-infected patients despite low CD4+ cell counts and CMV viremia: results of ACTG protocol A5030. *HIV Clin Trials*. May-Jun 2009;10(3):143-152. Available at http://www.ncbi.nlm.nih.gov/pubmed/19632953.

19. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. *N Engl J Med*. Apr 8 1999;340(14):1063-1070. Available at http://www.ncbi.nlm.nih.gov/pubmed/10194235.

20. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia J. Mortality risk for patients with cytomegalovirus retinitis and acquired immune deficiency syndrome. *Clin Infect Dis*. Nov 15 2003;37(10):1365-1373. Available at http://www.ncbi.nlm.nih.gov/pubmed/14583871.

21. Studies of Ocular Complications of ARGTACTG. The ganciclovir implant plus oral ganciclovir versus parenteral cidofovir for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome: The Ganciclovir Cidofovir Cytomegalovirus Retinitis Trial. *Am J Ophthalmol*. Apr 2001;131(4):457-467. Available at http://www.ncbi.nlm.nih.gov/pubmed/11292409.

22. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. *N Engl J Med*. Jul 10 1997;337(2):83-90. Available at http://www.ncbi.nlm.nih.gov/pubmed/9211677.

23. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med*. Apr 11 2002;346(15):1119-1126. Available at http://www.ncbi.nlm.nih.gov/pubmed/11948271.

24. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia JA. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. *Arch Ophthalmol*. Apr 2003;121(4):466-476. Available at http://www.ncbi.nlm.nih.gov/pubmed/12695243.

25. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. 4. Visual outcomes. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *Ophthalmology*. Jul 1994;101(7):1250-1261. Available at http://www.ncbi.nlm.nih.gov/pubmed/8035989.

26. Bowen EF, Wilson P, Cope A, et al. Cytomegalovirus retinitis in AIDS patients: influence of cytomegaloviral load on response to ganciclovir, time to recurrence and survival. *AIDS*. Nov 1996;10(13):1515-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/8931786.

27. Jabs DA, Ahuja A, Van Natta M, Dunn JP, Yeh S, Studies of the Ocular Complications of ARG. Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology*. Jun 2013;120(6):1262-1270. Available at http://www.ncbi.nlm.nih.gov/pubmed/23419804.

28. Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest*. Jan 15 1998;101(2):497-502. Available at http://www.ncbi.nlm.nih.gov/pubmed/9435323.

29. Jabs DA, Ahuja A, Van Natta M, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology*. Nov 2010;117(11):2152-2161 e2151-2152. Available at http://www.ncbi.nlm.nih.gov/pubmed/20673591.

30. Ortega-Larrocea G, Espinosa E, Reyes-Teran G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. *AIDS*. Apr 29 2005;19(7):735-738. Available at http://www.ncbi.nlm.nih.gov/pubmed/15821403.

31. Dubreuil-Lemaire ML, Gori A, Vittecoq D, et al. Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol*. Nov 2000;65(5):337-343. Available at http://www.ncbi.nlm.nih.gov/pubmed/11092465.

32. Kuritzkes DR, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. G-CSF 930101 Study Group. *AIDS*. Jan 1 1998;12(1):65-74. Available at http://www.ncbi.nlm.nih.gov/pubmed/9456256.

33. Nguyen QD, Kempen JH, Bolton SG, Dunn JP, Jabs DA. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. *Am J Ophthalmol*. May 2000;129(5):634-639. Available at http://www.ncbi.nlm.nih.gov/pubmed/10844056.

34. Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. *J Infect Dis*. Mar 1999;179(3):697-700. Available at http://www.ncbi.nlm.nih.gov/pubmed/9952380.

35. Robinson MR, Reed G, Csaky KG, Polis MA, Whitcup SM. Immune-recovery uveitis in patients with cytomegalovirus retinitis taking highly active antiretroviral therapy. *Am J Ophthalmol*. Jul 2000;130(1):49-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/11004259.

36. Karavellas MP, Song M, Macdonald JC, Freeman WR. Long-term posterior and anterior segment complications of immune recovery uveitis associated with cytomegalovirus retinitis. *Am J Ophthalmol*. Jul 2000;130(1):57-64. Available at http://www.ncbi.nlm.nih.gov/pubmed/11004260.

37. Kempen JH, Min YI, Freeman WR, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology*. Apr 2006;113(4):684-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/16581429.

38. Jabs DA, Ahuja A, Van Natta ML, et al. Long-term Outcomes of Cytomegalovirus Retinitis in the Era of Modern Antiretroviral Therapy: Results from a United States Cohort. *Ophthalmology*. Jul 2015;122(7):1452-1463. Available at http://www.ncbi.nlm.nih.gov/pubmed/25892019.

39. Jabs DA, Wingard JR, de Bustros S, de Miranda P, Saral R, Santos GW. BW B759U for cytomegalovirus retinitis: intraocular drug penetration. *Arch Ophthalmol*. Oct 1986;104(10):1436-1437. Available at http://www.ncbi.nlm.nih.gov/pubmed/3021090.

40. Morrison VL, Kozak I, LaBree LD, Azen SP, Kayicioglu OO, Freeman WR. Intravitreal triamcinolone acetonide for the treatment of immune recovery uveitis macular edema. *Ophthalmology*. Feb 2007;114(2):334-339. Available at http://www.ncbi.nlm.nih.gov/pubmed/17270681.

41. Ruiz-Cruz M, Alvarado-de la Barrera C, Ablanedo-Terrazas Y, Reyes-Teran G. Proposed clinical case definition for cytomegalovirus-immune recovery retinitis. *Clin Infect Dis*. Jul 15 2014;59(2):298-303. Available at http://www.ncbi.nlm.nih.gov/pubmed/24771331.

42. Holland GN, Vaudaux JD, Shiramizu KM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. II. Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol*. Jan 2008;145(1):12-22.

Available at http://www.ncbi.nlm.nih.gov/pubmed/18154751.

43. Kuppermann BD, Quiceno JI, Flores-Aguilar M, et al. Intravitreal ganciclovir concentration after intravenous administration in AIDS patients with cytomegalovirus retinitis: implications for therapy. *J Infect Dis*. Dec 1993;168(6):1506-1509. Available at http://www.ncbi.nlm.nih.gov/pubmed/8245536.
44. Arevalo JF, Gonzalez C, Capparelli EV, et al. Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis*. Oct 1995;172(4):951-956. Available at http://www.ncbi.nlm.nih.gov/pubmed/7561215.
45. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The Cytomegalovirus Retreatment Trial. The Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. *Arch Ophthalmol*. Jan 1996;114(1):23-33. Available at http://www.ncbi.nlm.nih.gov/pubmed/8540847.
46. Jabs DA, Enger C, Dunn JP, Forman M. Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. CMV Retinitis and Viral Resistance Study Group. *J Infect Dis*. Mar 1998;177(3):770-773. Available at http://www.ncbi.nlm.nih.gov/pubmed/9498461.
47. Jabs DA, Enger C, Forman M, Dunn JP. Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. The Cytomegalovirus Retinitis and Viral Resistance Study Group. *Antimicrob Agents Chemother*. Sep 1998;42(9):2240-2244. Available at http://www.ncbi.nlm.nih.gov/pubmed/9736542.
48. Jabs DA, Martin BK, Forman MS, et al. Mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis*. Jan 15 2001;183(2):333-337. Available at http://www.ncbi.nlm.nih.gov/pubmed/11120934.
49. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. *Proc Natl Acad Sci USA*. Jul 5 2000;97(14):8039-8044. Available at http://www.ncbi.nlm.nih.gov/pubmed/10859361.
50. Jabs DA, Enger C, Dunn JP, Forman M, Hubbard L. Cytomegalovirus retinitis and viral resistance: 3. Culture results. CMV Retinitis and Viral Resistance Study Group. *Am J Ophthalmol*. Oct 1998;126(4):543-549. Available at http://www.ncbi.nlm.nih.gov/pubmed/9780099.
51. Weinberg A, Jabs DA, Chou S, et al. Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis*. Mar 1 2003;187(5):777-784. Available at http://www.ncbi.nlm.nih.gov/pubmed/12599051.
52. Martin BK, Ricks MO, Forman MS, Jabs DA, Cytomegalovirus R, Viral Resistance Study G. Change over time in incidence of ganciclovir resistance in patients with cytomegalovirus retinitis. *Clin Infect Dis*. Apr 1 2007;44(7):1001-1008. Available at http://www.ncbi.nlm.nih.gov/pubmed/17342657.
53. Chou S, Erice A, Jordan MC, et al. Analysis of the UL97 phosphotransferase coding sequence in clinical cytomegalovirus isolates and identification of mutations conferring ganciclovir resistance. *J Infect Dis*. Mar 1995;171(3):576-583. Available at http://www.ncbi.nlm.nih.gov/pubmed/7876604.
54. Chou S, Guentzel S, Michels KR, Miner RC, Drew WL. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. *J Infect Dis*. Jul 1995;172(1):239-242. Available at http://www.ncbi.nlm.nih.gov/pubmed/7797920.
55. Smith IL, Cherrington JM, Jiles RE, Fuller MD, Freeman WR, Spector SA. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. *J Infect Dis*. Jul 1997;176(1):69-77. Available at http://www.ncbi.nlm.nih.gov/pubmed/9207351.
56. Chou S, Lurain NS, Thompson KD, Miner RC, Drew WL. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. *J Infect Dis*. Jul 1 2003;188(1):32-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/12825168.
57. Chou S, Van Wechel LC, Lichy HM, Marousek GI. Phenotyping of cytomegalovirus drug resistance mutations by using recombinant viruses incorporating a reporter gene. *Antimicrob Agents Chemother*. Jul 2005;49(7):2710-2715. Available at http://www.ncbi.nlm.nih.gov/pubmed/15980340.
58. Wolf DG, Smith IL, Lee DJ, Freeman WR, Flores-Aguilar M, Spector SA. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. *J Clin Invest*. Jan 1995;95(1):257-263. Available at http://www.ncbi.nlm.nih.gov/pubmed/7814623.
59. Vitravene Study G. Randomized dose-comparison studies of intravitreous fomivirsen for treatment of cytomegalovirus retinitis that has reactivated or is persistently active despite other therapies in patients with AIDS. *Am J Ophthalmol*. Apr 2002;133(4):475-483. Available at http://www.ncbi.nlm.nih.gov/pubmed/11931781.

60. Jabs DA, Martin BK, Ricks MO, Forman MS, Cytomegalovirus R, Viral Resistance Study G. Detection of ganciclovir resistance in patients with AIDS and cytomegalovirus retinitis: correlation of genotypic methods with viral phenotype and clinical outcome. *J Infect Dis*. Jun 15 2006;193(12):1728-1737. Available at http://www.ncbi.nlm.nih.gov/pubmed/16703517.

61. Jabs DA, Martin BK, Forman MS, et al. Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. *Am J Ophthalmol*. Jan 2003;135(1):26-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/12504693.

62. Jabs DA, Martin BK, Forman MS, Cytomegalovirus R, Viral Resistance Research G. Mortality associated with resistant cytomegalovirus among patients with cytomegalovirus retinitis and AIDS. *Ophthalmology*. Jan 2010;117(1):128-132 e122. Available at http://www.ncbi.nlm.nih.gov/pubmed/19818505.

63. AIDS Clinical Trials Group (ACTG) SoocoAF-GCRTR, design, and methods. AIDS Clinical Trials Group (ACTG),. Studies of ocular complications of AIDS Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 1. Rationale, design, and methods. AIDS Clinical Trials Group (ACTG). *Control Clin Trials*. Feb 1992;13(1):22-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/1315661.

64. Taskintuna I, Rahhal FM, Rao NA, et al. Adverse events and autopsy findings after intravitreous cidofovir (HPMPC) therapy in patients with acquired immune deficiency syndrome (AIDS). *Ophthalmology*. Nov 1997;104(11):1827-1836; discussion 1836-1827. Available at http://www.ncbi.nlm.nih.gov/pubmed/9373113.

65. Holbrook JT, Colvin R, van Natta ML, et al. Evaluation of the United States public health service guidelines for discontinuation of anticytomegalovirus therapy after immune recovery in patients with cytomegalovirus retinitis. *Am J Ophthalmol*. Oct 2011;152(4):628-637 e621. Available at http://www.ncbi.nlm.nih.gov/pubmed/21742304.

66. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis*. Apr 1998;177(4):1080-1083. Available at http://www.ncbi.nlm.nih.gov/pubmed/9534987.

67. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. *Ophthalmology*. Jul 1998;105(7):1259-1264. Available at http://www.ncbi.nlm.nih.gov/pubmed/9663231.

68. Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis*. May 1998;177(5):1182-1187. Available at http://www.ncbi.nlm.nih.gov/pubmed/9593001.

69. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. *JAMA*. Nov 3 1999;282(17):1633-1637. Available at http://www.ncbi.nlm.nih.gov/pubmed/10553789.

70. Jabs DA, Bolton SG, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. *Am J Ophthalmol*. Dec 1998;126(6):817-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/9860006.

71. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Jan 5 2001;15(1):23-31. Available at http://www.ncbi.nlm.nih.gov/pubmed/11192865.

72. Walmsley SL, Raboud J, Angel JB, et al. Long-term follow-up of a cohort of HIV-infected patients who discontinued maintenance therapy for cytomegalovirus retinitis. *HIV Clin Trials*. Jan-Feb 2006;7(1):1-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/16632459.

73. Torriani FJ, Freeman WR, Macdonald JC, et al. CMV retinitis recurs after stopping treatment in virological and immunological failures of potent antiretroviral therapy. *AIDS*. Jan 28 2000;14(2):173-180. Available at http://www.ncbi.nlm.nih.gov/pubmed/10708288.

74. Faqi AS, Klug A, Merker HJ, Chahoud I. Ganciclovir induces reproductive hazards in male rats after short-term exposure. *Hum Exp Toxicol*. Sep 1997;16(9):505-511. Available at http://www.ncbi.nlm.nih.gov/pubmed/9306137.

75. Miller BW, Howard TK, Goss JA, Mostello DJ, Holcomb WL, Jr., Brennan DC. Renal transplantation one week after conception. *Transplantation*. Dec 15 1995;60(11):1353-1354. Available at http://www.ncbi.nlm.nih.gov/pubmed/8525535.

76. Pescovitz MD. Absence of teratogenicity of oral ganciclovir used during early pregnancy in a liver transplant recipient. *Transplantation*. Mar 15 1999;67(5):758-759. Available at http://www.ncbi.nlm.nih.gov/pubmed/10096536.

77. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. *Semin Perinatol*. Feb 2007;31(1):10-18. Available at http://www.ncbi.nlm.nih.gov/pubmed/17317422.

78. Alvarez-McLeod A, Havlik J, Drew KE. Foscarnet treatment of genital infection due to acyclovir-resistant herpes simplex virus type 2 in a pregnant patient with AIDS: case report. *Clin Infect Dis*. Oct 1999;29(4):937-938. Available at http://www.ncbi.nlm.nih.gov/pubmed/10589917.

79. Yamamoto AY, Mussi-Pinhata MM, Boppana SB, et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. *Am J Obstet Gynecol*. Mar 2010;202(3):297 e291-298. Available at http://www.ncbi.nlm.nih.gov/pubmed/20060091.

80. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. *JAMA*. Oct 10 1986;256(14):1904-1908. Available at http://www.ncbi.nlm.nih.gov/pubmed/3020264.

81. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med*. Jul 8 1999;341(2):77-84. Available at http://www.ncbi.nlm.nih.gov/pubmed/10395631.

82. Quinn TC, Piot P, McCormick JB, et al. Serologic and immunologic studies in patients with AIDS in North America and Africa. The potential role of infectious agents as cofactors in human immunodeficiency virus infection. *JAMA*. May 15 1987;257(19):2617-2621. Available at http://www.ncbi.nlm.nih.gov/pubmed/3494857.

83. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT, Cervi MC, Duarte G. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. *J Pediatr*. Feb 1998;132(2):285-290. Available at http://www.ncbi.nlm.nih.gov/pubmed/9506642.

84. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. *Am J Obstet Gynecol*. May 1988;158(5):1189-1195. Available at http://www.ncbi.nlm.nih.gov/pubmed/2835906.

85. Duryea EL, Sanchez PJ, Sheffield JS, et al. Maternal human immunodeficiency virus infection and congenital transmission of cytomegalovirus. *Pediatr Infect Dis J*. Oct 2010;29(10):915-918. Available at http://www.ncbi.nlm.nih.gov/pubmed/20431424.

86. Guibert G, Warszawski J, Le Chenadec J, et al. Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Jun 1 2009;48(11):1516-1525. Available at http://www.ncbi.nlm.nih.gov/pubmed/19388872.

87. Frederick T, Homans J, Spencer L, et al. The effect of prenatal highly active antiretroviral therapy on the transmission of congenital and perinatal/early postnatal cytomegalovirus among HIV-infected and HIV-exposed infants. *Clin Infect Dis*. Sep 2012;55(6):877-884. Available at http://www.ncbi.nlm.nih.gov/pubmed/22675157.

88. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. Feb 2006;35(2):226-231. Available at http://www.ncbi.nlm.nih.gov/pubmed/16386462.

89. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol*. Sep 1996;175(3 Pt 1):661-667. Available at http://www.ncbi.nlm.nih.gov/pubmed/8828431.

90. Ekoukou D, Khuong-Josses MA, Ghibaudo N, Mechali D, Rotten D. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. *Eur J Obstet Gynecol Reprod Biol*. Oct 2008;140(2):212-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/18584937.

91. Maiques V, Garcia-Tejedor A, Perales A, Cordoba J, Esteban RJ. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women? *Eur J Obstet Gynecol Reprod Biol*. Jun 10 2003;108(2):137-141. Available at http://www.ncbi.nlm.nih.gov/pubmed/12781400.

92. Nigro G, Adler SP, La Torre R, Best AM, Congenital Cytomegalovirus Collaborating G. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med*. Sep 29 2005;353(13):1350-1362. Available at http://www.ncbi.nlm.nih.gov/pubmed/16192480.

93. Nigro G, Torre RL, Pentimalli H, et al. Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy. *Prenat Diagn*. Jun 2008;28(6):512-517. Available at http://www.ncbi.nlm.nih.gov/pubmed/18509871.

94. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med*. Apr 3 2014;370(14):1316-1326. Available at http://www.ncbi.nlm.nih.gov/pubmed/24693891.

Herpes Simplex Virus Disease (Last updated September 17, 2015; last reviewed September 17, 2015)

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common, with a seroprevalence of HSV-1 among adults in the United States of approximately 60% and a seroprevalence of HSV-2 among persons aged ≥12 years of 17%.[1] Approximately 70% of HIV-infected persons are HSV-2 seropositive and 95% are seropositive for either HSV-1 or HSV-2.[2] In most persons, HSV infections are unrecognized clinically. However, regardless of the clinical severity of infection, shedding on mucosal surfaces occurs frequently and can result in transmission. HSV-2 infection increases the risk of HIV acquisition two- to three-fold, and HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions of coinfected patients.

Clinical Manifestations

Orolabial herpes (e.g., cold sores, fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations include a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lip. The course of illness in untreated patients is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is the most common manifestation of HSV-2 infection. Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on genital skin (e.g., the penile shaft, thighs, pubis). Local symptoms might include a sensory prodrome consisting of pain and pruritis. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[3] These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized, not brought to medical attention, and cannot reliably be diagnosed by physical examination. HSV is a significant cause of proctitis in men who have sex with men with HIV infection and may not be associated with external anal ulcers.[4] In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 T-lymphocyte (CD4) cell counts of <100 cells/μL and also may be associated with acyclovir-resistant HSV.[5] In addition, atypical presentations such as hypertrophic genital HSV,[6,7] which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but genital HSV-1 recurrences and viral shedding occur less often than with genital HSV-2 infection.

Non-mucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to manifestations observed in HIV-seronegative individuals; disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, especially in persons with HIV infection, a laboratory diagnosis should be pursued in all cases.[8] HSV DNA polymerase chain reaction (PCR), and viral culture are preferred methods for diagnosis of mucocutaneous HSV lesions caused by HSV. PCR is the most sensitive method. The virus detected in genital lesions should be typed because of the prognostic significance—HSV-1 recurs less frequently than HSV-2 in the genital area. Type-specific serologic assays are commercially available and can be used for diagnosis in asymptomatic individuals or those with atypical lesions. Because of the poor sensitivity and specificity of clinical diagnosis,

the extensive interactions between HIV and HSV-2, and the availability of effective therapy for HSV-2, routine type-specific serologic screening for HSV-2 for persons with HIV infection can be considered. Diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2015 Centers for Disease Control and Prevention sexually-transmitted disease treatment guidelines.[9]

Preventing Exposure

The majority of persons with HIV infection have HSV-1 and HSV-2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. Persons with HIV infection who are HSV-2 seronegative should consider asking their partners to be tested using type-specific serology before initiating sexual activity, because disclosure of HSV-2 in heterosexual HIV-negative HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 **(BII)**.[10] Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens **(AII)**.[11,12] Persons with HIV infection should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions **(AII)**. However, most sexual transmission of HSV occurs during asymptomatic viral shedding.

The use of suppressive antiviral therapy (i.e., valacyclovir 500 mg once daily) in persons without HIV infection with symptomatic genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 48%.[13] However, in HIV-1/HSV-2-seropositive persons not on antiretroviral therapy, suppressive acyclovir (400 mg twice daily) did not prevent HSV-2 transmission to HSV-2 seronegative partners.[14] Suppressive anti-HSV therapy is not recommended to prevent HSV-2 transmission in persons with HIV infection who are not on ART **(AI)**.

Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection is not recommended **(AIII)**. Although preexposure prophylaxis (PrEP) with vaginal tenofovir and oral tenofovir or tenofovir/emtricitabine has been associated with reduced risk of HSV-2 acquisition in clinical trials in HIV-negative persons[15,16], vaginal and oral tenofovir for prevention of HSV-2 has not been studied in persons with HIV infection. The dose, duration, timing, and efficacy of antiviral prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available.

Treating Disease

Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. The management plan for genital HSV-2 disease in persons with HIV infection should include consideration of several factors, such as frequency and severity of HSV recurrences, and risk for genital ulcer disease (GUD) when initiating ART. Episodic treatment for individual recurrences does not influence the natural history of genital HSV-2 infection.

Patients with orolabial lesions can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 to 10 days **(AIII)**. Genital HSV episodes should be treated with oral acyclovir, valacyclovir, or famciclovir for 5 to 10 days **(AI)**. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir **(AIII)**.[5,17] Patients can be switched to oral antiviral therapy after their lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Disseminated disease due to HSV is rare in persons with HIV infection, although HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus (VZV).

Special Considerations with Regard to Starting Antiretroviral Therapy

In most instances, orolabial HSV should not influence the decision about when to start antiretroviral therapy (ART). Persons with HIV infection receiving ART who have had immune reconstitution often have

improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[18] Chronic cutaneous or muscosal HSV that is refractory to therapy and visceral or disseminated cases of HSV disease (which are uncommon) would be indications to hasten the initiation of ART **(CIII)**.

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome [IRIS])

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless they have advanced renal impairment. For patients receiving high-dose IV acyclovir, monitoring of renal function and dose adjustment as necessary are recommended at initiation of treatment and once or twice weekly for the duration of treatment. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in persons with HIV infection treated with high-dose (8 g/day) valacyclovir, but has not been reported at conventional doses recommended for therapy of HSV infection.[19]

HSV-2 shedding and genital ulcer disease can increase in the first 6 months after initiation of ART, particularly in those with low CD4 cell count.[20,21] Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to immune reconstitution inflammatory syndrome (IRIS).[22]

Managing Treatment Failure

Treatment failure as a result of resistance to antivirals should be suspected if lesions do not begin to resolve within 7 to 10 days after initiation of therapy. In persons with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance **(AII)**.[23] Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is not yet available.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI)**.[24,25] IV cidofovir is a potential alternative **(CIII)**. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer may be required **(CIII)**.

Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences **(AI)**.[8,26] Suppressive therapy for HSV may be continued indefinitely, without regard for improved CD4 cell count, although need for continuation should be addressed on an annual basis, particularly if immune reconstitution has occurred **(BIII)**. In persons starting ART with CD4 cell counts <250 cells/mm^3, there is in increased risk of HSV-2 shedding and genital ulcer disease in the first 6 months; suppressive ACV decreases the risk of GUD nearly 60% compared to placebo, and may be recommended for persons with CD4 cell counts <250 cells/mm^3 starting ART **(BI)**.

Suppressive anti-HSV therapy in persons with HIV infection not on ART also results in a decrease in plasma, anal, and genital secretion HIV RNA levels and in a lower risk of HIV progression.[27] However, antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners, and should not be used to delay HIV progression in place of ART when ART is available.[28] In persons who are taking ART, suppressive HSV antivirals do not impact HIV progression, improve in CD4 T-cell recovery, or decrease markers of systemic inflammation[29,30] and should not be used for this purpose **(AI)**.

The use of daily suppressive therapy (when compared to episodic therapy) has been associated with a lower risk of development of acyclovir-resistant HSV in hematopoietic stem cell recipients;[31] there are no specific data for persons with HIV infection.

Special Considerations During Pregnancy

Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease during HSV acquistion is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe **(AIII)**.[32] The use of valacyclovir and famciclovir during pregnancy has been described and they appear to be safe and well tolerated.[33] Valacyclovir use can be considered for treatment and suppressive therapy during pregnancy because of its simplified dosing schedule **(CIII)**.

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of HSV transmission to the newborn in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV late in pregnancy. The adverse sequelae for the neonate, however, can be very significant. The predominant risk for HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(BII)**.[8] Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women[34] and is likely to have similar efficacy in women with HIV infection. However, neonatal HSV disease has been reported in women treated with suppressive antiviral therapy.[35] Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy **(BII)**.[36] Suppressive therapy for women who are only seropositive for HSV-2 without a history of genital lesions is not recommended. Maternal genital herpes was a risk factor for perinatal mother-to-child HIV transmission in the pre-highly active antiretroviral therapy era.[37] Whether HSV facilitates HIV transmission among pregnant women on ART is unknown.

Recommendations for Treating Herpes Simplex Virus (HSV) Infections (page 1 of 2)

Treating Orolabial Lesions (Duration: 5–10 days)

- Valacyclovir 1 g PO BID **(AIII)**, *or*
- Famciclovir 500 mg PO BID **(AIII)**, *or*
- Acyclovir 400 mg PO TID **(AIII)**

Treating Initial or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO TID **(AI)**

Treating Severe Mucocutaneous HSV Infections (AIII)

- Initial therapy acyclovir 5 mg/kg IV q8h
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Chronic Suppressive Therapy

Indications:

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**, *or*
- To reduce the risk of GUD in patients with CD4 cell counts <250 cells/mm^3 who are starting ART **(BI)**

Treatment:

- Valacyclovir 500 mg PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO BID **(AI)**
- Evaluate ongoing need for suppressive therapy annually.

Recommendations for Treating Herpes Simplex Virus (HSV) Infections (page 2 of 2)

For Acyclovir-Resistant Mucocutaneous HSV infections

Preferred Therapy:

- Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)**

Alternative Therapy (Duration: 21–28 days or longer, based on clinical response) **(CIII)**:

- Topical trifluridine, *or*
- Topical cidofovir 1% gel, *or*
- Topical imiquimod 5% cream three times/week, *or*
- IV cidofovir 5 mg/kg IV once weekly

Note:

- Topical formulations of trifluridine and cidofovir are not commercially available.
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

Key to Acronyms: BID = twice daily; GUD = genital ulcer disease; HSV = herpes simplex virus; IV = intraveneously; PO = orally; TID = three times daily

References

1. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. Aug 23 2006;296(8):964-973. Available at http://www.ncbi.nlm.nih.gov/pubmed/16926356.
2. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):435-445. Available at http://www.ncbi.nlm.nih.gov/pubmed/15021308.
3. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*. Jun 1983;98(6):958-972. Available at http://www.ncbi.nlm.nih.gov/pubmed/6344712.
4. Bissessor M, Fairley CK, Read T, Denham I, Bradshaw C, Chen M. The etiology of infectious proctitis in men who have sex with men differs according to HIV status. *Sex Transm Dis*. Oct 2013;40(10):768-770. Available at http://www.ncbi.nlm.nih.gov/pubmed/24275725.
5. Safrin S, Elbeik T, Phan L, et al. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. Jun 1994;38(6):1246-1250. Available at http://www.ncbi.nlm.nih.gov/pubmed/8092821.
6. Yudin MH, Kaul R. Progressive hypertrophic genital herpes in an HIV-infected woman despite immune recovery on antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2008;2008:592532. Available at http://www.ncbi.nlm.nih.gov/pubmed/18784844.
7. Sbidian E, Battistella M, Legoff J, et al. Recalcitrant pseudotumoral anogenital herpes simplex virus type 2 in HIV-infected patients: evidence for predominant B-lymphoplasmocytic infiltration and immunomodulators as effective therapeutic strategy. *Clin Infect Dis*. Dec 2013;57(11):1648-1655. Available at http://www.ncbi.nlm.nih.gov/pubmed/24065320.
8. Workowski KA, Berman S, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160459.
9. Workowski KA, Bolan GA, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. Jun 5 2015;64(RR-03):1-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/26042815.
10. Wald A, Krantz E, Selke S, Lairson E, Morrow RA, Zeh J. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis*. Jul 1 2006;194(1):42-52. Available at http://www.ncbi.nlm.nih.gov/pubmed/16741881.
11. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. Nov 15 2005;143(10):707-713. Available at http://www.ncbi.nlm.nih.gov/pubmed/16287791.
12. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. Jul 13 2009;169(13):1233-1240. Available at http://www.ncbi.nlm.nih.gov/pubmed/19597073.

13. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. Jan 1 2004;350(1):11-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/14702423.
14. Mujugira A, Magaret AS, Celum C, et al. Daily acyclovir to decrease herpes simplex virus type 2 (HSV-2) transmission from HSV-2/HIV-1 coinfected persons: a randomized controlled trial. *J Infect Dis*. Nov 1 2013;208(9):1366-1374. Available at http://www.ncbi.nlm.nih.gov/pubmed/23901094.
15. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. Sep 3 2010;329(5996):1168-1174. Available at http://www.ncbi.nlm.nih.gov/pubmed/20643915.
16. Celum C, Morrow RA, Donnell D, et al. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. *Ann Intern Med*. Jul 1 2014;161(1):11-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/24979446.
17. Meyers JD, Wade JC, Mitchell CD, et al. Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. *Am J Med*. Jul 20 1982;73(1A):229-235. Available at http://www.ncbi.nlm.nih.gov/pubmed/7048914.
18. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. *J Infect Dis*. Aug 15 2004;190(4):693-696. Available at http://www.ncbi.nlm.nih.gov/pubmed/15272395.
19. Bell WR, Chulay JD, Feinberg JE. Manifestations resembling thrombotic microangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). *Medicine (Baltimore)*. Sep 1997;76(5):369-380. Available at http://www.ncbi.nlm.nih.gov/pubmed/9352739.
20. Graham SM, Masese L, Gitau R, et al. Increased risk of genital ulcer disease in women during the first month after initiating antiretroviral therapy. *J Acquir Immune Defic Syndr*. Dec 2009;52(5):600-603. Available at http://www.ncbi.nlm.nih.gov/pubmed/19648822.
21. Tobian AA, Grabowski MK, Serwadda D, et al. Reactivation of herpes simplex virus type 2 after initiation of antiretroviral therapy. *J Infect Dis*. Sep 1 2013;208(5):839-846. Available at http://www.ncbi.nlm.nih.gov/pubmed/23812240.
22. Couppie P, Sarazin F, Clyti E, et al. Increased incidence of genital herpes after HAART initiation: a frequent presentation of immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients. *AIDS Patient Care STDS*. Mar 2006;20(3):143-145. Available at http://www.ncbi.nlm.nih.gov/pubmed/16548710.
23. Balfour HH, Jr. Antiviral drugs. *N Engl J Med*. Apr 22 1999;340(16):1255-1268. Available at http://www.ncbi.nlm.nih.gov/pubmed/10210711.
24. Safrin S, Crumpacker C, Chatis P, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. The AIDS Clinical Trials Group. *N Engl J Med*. Aug 22 1991;325(8):551-555. Available at http://www.ncbi.nlm.nih.gov/pubmed/1649971.
25. Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. *Clin Infect Dis*. Nov 1 2004;39 Suppl 5:S248-257. Available at http://www.ncbi.nlm.nih.gov/pubmed/15494896.
26. DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis*. Oct 1 2003;188(7):1009-1016. Available at http://www.ncbi.nlm.nih.gov/pubmed/14513421.
27. Lingappa JR, Baeten JM, Wald A, et al. Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet*. Mar 6 2010;375(9717):824-833. Available at http://www.ncbi.nlm.nih.gov/pubmed/20153888.
28. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. Feb 4 2010;362(5):427-439. Available at http://www.ncbi.nlm.nih.gov/pubmed/20089951.
29. Yi TJ, Walmsley S, Szadkowski L, et al. A randomized controlled pilot trial of valacyclovir for attenuating inflammation and immune activation in HIV/herpes simplex virus 2-coinfected adults on suppressive antiretroviral therapy. *Clin Infect Dis*. Nov 2013;57(9):1331-1338. Available at http://www.ncbi.nlm.nih.gov/pubmed/23946220.
30. Van Wagoner N, Geisler WM, Bachmann LH, Hook EW. The effect of valacyclovir on HIV and HSV-2 in HIV-infected persons on antiretroviral therapy with previously unrecognised HSV-2. *Int J STD AIDS*. Aug 21 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/25147236.

31. Erard V, Wald A, Corey L, Leisenring WM, Boeckh M. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. *J Infect Dis*. Jul 15 2007;196(2):266-270. Available at http://www.ncbi.nlm.nih.gov/pubmed/17570114.

32. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol*. Apr 2004;70(4):201-207. Available at http://www.ncbi.nlm.nih.gov/pubmed/15108247.

33. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. Aug 25 2010;304(8):859-866. Available at http://www.ncbi.nlm.nih.gov/pubmed/20736469.

34. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol*. Dec 2003;102(6):1396-1403. Available at http://www.ncbi.nlm.nih.gov/pubmed/14662233.

35. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr*. Jul 2012;161(1):134-138 e131-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/22336576.

36. Bulletins--Gynecology ACoP. ACOG Practice Bulletin No. 117: Gynecologic care for women with human immunodeficiency virus. *Obstet Gynecol*. Dec 2010;116(6):1492-1509. Available at http://www.ncbi.nlm.nih.gov/pubmed/21099636.

37. Chen KT, Segu M, Lumey LH, et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. *Obstet Gynecol*. Dec 2005;106(6):1341-1348. Available at http://www.ncbi.nlm.nih.gov/pubmed/16319261.

Varicella-Zoster Virus Diseases (Last updated July 8, 2013; last reviewed July 8, 2013)

Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella, the vast majority due to primary VZV infection, known as varicella (or chickenpox). Reactivation of latent VZV results in herpes zoster (or shingles). A person's lifetime risk for herpes zoster is 15% to 20%, with the highest incidence occurring in the elderly and immunocompromised individuals. The incidence of herpes zoster is >15-fold higher for HIV-infected adults than for age-matched controls.[1] Herpes zoster can occur in HIV-infected adults at any CD4 T lymphocyte (CD4) cell count, but frequency of disease is highest with CD4 counts of <200 cells/μL.[2-4] Antiretroviral therapy (ART) has not been shown to reduce the incidence of herpes zoster in adult populations: in fact, rates appear to be higher in the period immediately after initiation of ART. Lower frequency of herpes zoster in pediatric patients treated with ART has been observed, but it is difficult to separate ART effect from the impact of varicella vaccine.[5,6]

Clinical Manifestations

Varicella rash tends to have a central distribution with lesions first appearing on the head, then trunk, and finally the extremities, evolving through stages of macules, papules, vesicles, pustules, and crusts. The rash is characterized by rapid evolution of lesions during the initial 8 to 12 hours and by successive crops of new lesions and by the presence of lesions in different stages of development at the same time. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise, and anorexia.[7] Primary varicella can cause substantial morbidity in HIV-seropositive adolescents and adults. Visceral dissemination, especially VZV pneumonitis, is well documented.[7] Because most HIV-infected adults in the United States are VZV seropositive, primary varicella is an uncommon occurrence in this population.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40%–50% of cases), followed by cranial nerve (20%–25%), cervical (15%–20%), lumbar (15%), and sacral (5%) dermatomes. Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain (which may be severe). New vesicle formation typically continues for 3 to 5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2 to 3 weeks. About 20% to 30% of HIV-infected patients have one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%.[3,8] Approximately 10% to 15% of HIV-seropositive patients report post-herpetic neuralgia as a complication following herpes zoster.[3,9]

Most herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, occur in patients with CD4 counts of <200 cells/μL.[10] The CNS is the primary target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively in AIDS patients with CD4 counts <100 cells/μL.[11] In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of retinal vasculitis, and multiple discrete peripheral lesions in the outer retinal layer.[12] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[13] Both ARN and PORN are associated with high rates of visual loss.

Diagnosis

Varicella and herpes zoster are distinctive in appearance and diagnosis can usually be made clinically. Varicella can also be diagnosed retrospectively by documenting seroconversion. Immunocompromised persons can have atypical presentations and varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); history of varicella or VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful. When lesions are atypical or the diagnosis of VZV from other exanthems is uncertain, swabs from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase chain reaction (PCR). Additionally, scabs are very good specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections. Histopathology and PCR (of blood or fluids such as cerebrospinal fluid or vitreous humor) can aid with diagnosis of VZV infections of visceral organs (e.g., pneumonitis, encephalitis, retinitis).[14] Routine serologic testing to determine the VZV serologic status of HIV-infected adults is not recommended.

Preventing Exposure

HIV-infected persons who are susceptible to VZV (i.e., persons who have no history of varicella or shingles, who are seronegative for VZV, and who have no history of vaccination against VZV) should avoid exposure to individuals with varicella or herpes zoster **(AII)**.

If household contacts of HIV-infected persons without evidence of immunity to varicella are themselves without evidence of immunity, then these household contacts should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to their susceptible HIV-infected contacts **(BIII)**.

Preventing Disease

Long-term prophylaxis with antiviral drugs to prevent varicella is not recommended **(AIII)**. Rather, for HIV-infected persons who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended.

Vaccination To Prevent Primary Infection

The live attenuated varicella vaccine has been documented to be safe and immunogenic in HIV-infected children with relatively preserved immune systems (CD4 lymphocyte percentage ≥15%)[15-18] and is recommended for them **(AI)**.[19] Varicella vaccination of HIV-seropositive children also reduces the risk of subsequent herpes zoster.[6,18] No studies have evaluated the vaccine in HIV-infected adolescents or adults, but varicella vaccination (2 doses, administered 3 months apart) may be considered in HIV-seropositive/VZV-seronegative persons ≥8 years old with CD4 counts ≥200 cells/μL **(CIII)**.[20] If vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir is recommended **(AIII)**. Administration of varicella vaccine to more severely immunocompromised HIV-infected patients (CD4 counts <200 cells/μL) is not recommended **(AIII)**. Because of the high prevalence of VZV seropositivity in adults, use of varicella vaccine in this population will be infrequent. If post-exposure varicella-zoster immune globulin (VariZIG™) has been administered, an interval of at least 5 months is recommended before varicella vaccination **(CIII)**.[21] If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination **(CIII)**.

Post-Exposure Prophylaxis To Prevent Primary Infection

After close contact with a person who has active varicella or herpes zoster, HIV-infected adolescents and adults who are susceptible to VZV should receive VariZIG as soon as possible, but within 10 days after exposure **(AIII)**.[22] Risk for VZV transmission is higher following exposure to a person with varicella than after exposure to localized herpes zoster. In the United States, VariZIG can be obtained only under a treatment investigational new drugs application (IND) by contacting FFF Enterprises (Temecula, CA), at (800) 843-7477. The duration of protection is at least 3 weeks. Patients receiving monthly high-dose

intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before exposure. Short-term post-exposure administration of acyclovir or valacyclovir beginning 7 to 10 days after exposure[23] may be considered for preventing varicella among susceptible HIV-infected adolescents or adults but this intervention has not been studied in these populations **(BIII)**. Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for varicella and is more effective than pre-emptive therapy with antiviral drugs; however the efficacy of post-exposure varicella vaccination for adolescents and adults has also not been established.

Treating Disease

Varicella

No controlled prospective studies of antiviral therapy for varicella in HIV-infected adults have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO 3 times daily), or famciclovir (500 mg PO 3 times daily) for 5 to 7 days **(AII)**. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg 5 times daily) can be an alternative **(BII)**. Intravenous (IV) acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe varicella **(AIII)**.[7,24,25] If no evidence of visceral involvement with VZV is apparent, switching to oral antiviral therapy after the patient has defervesced may be permissible **(BIII)**.[26]

Herpes Zoster

Prompt antiviral therapy should be instituted in all HIV-seropositive patients whose herpes zoster is diagnosed within 1 week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected cpatients are oral valacyclovir **(AII)**, famciclovir **(AII)**, or acyclovir **(BII)** (doses as above) for 7 to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident **(AII)**.[27] A switch from IV acyclovir to oral antiviral therapy (to complete a 10- to 14-day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving **(BIII)**. Because of the absence of data to support benefit in this population, adjunctive corticosteroid therapy for herpes zoster is not recommended **(AIII)**. Optimization of ART is recommended for all patients with VZV infections that are difficult to treat (e.g., retinitis, encephalitis) **(AIII)**.

Optimal antiviral therapy for PORN remains undefined.[28-30] Outcomes with intravenous acyclovir or ganciclovir monotherapy were poor. Better results were obtained with intravenous ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.[29] Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet) **(AIII)**.[31,32] Treatment regimens for PORN recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet ***plus*** intravitreal injections of ganciclovir and/or foscarnet **(AIII)**. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

Optimization of ART in HIV-infected patients with PORN is also recommended **(AIII)**.[32] Anecdotal reports have described success with IV cidofovir for PORN. Intravitreal cidofovir should not be used because such injections may be associated with loss of intraocular pressure and other adverse effects. Ganciclovir ocular implants, previously recommended by some experts, are no longer manufactured.

ARN appears to be more responsive than PORN to antiviral therapy. One recommended treatment is high-dose IV acyclovir (10–15 mg/kg every 8 hours for 10–14 days), followed by prolonged oral valacyclovir (1 gram 3 times daily for 6 weeks) **(AIII)**. Many experts would also include 1 or 2 doses of intravitreal ganciclovir as part of the initial induction therapy **(BIII)**. Involvement of an experienced ophthalmologist in

management of patients with VZV retinitis is strongly recommended **(AIII)**.

When to Start ART

A single uncomplicated episode of herpes zoster in an HIV-infected individual is not an indication to initiate ART nor is it an indication to defer ART. Initiation of ART should be strongly considered in a patient who has multiple recurrences of herpes zoster or who has a complication of VZV disease (e.g., PORN, encephalitis) **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding sections on herpes simplex virus and cytomegalovirus.

Immune reconstitution following initiation of ART appears to be associated with an increased frequency of VZV reactivation.[33-36] Observational studies have shown the risk of zoster to increase 2- to 4-fold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution do not differ from those observed in other HIV-infected patients and such episodes should be managed in the same manner.

Managing Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir (and related drugs) is rare, but should be suspected if clinical findings do not improve within 10 days of initiation of therapy or if skin lesions have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to establish antiviral drug susceptibility or resistance and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended **(AII)**.[37] IV cidofovir is a potential alternative **(AIII)**.

Preventing Recurrence

The efficacy of long-term antiviral prophylaxis to prevent herpes zoster recurrences in HIV-seropositive persons has not been evaluated and is not routinely recommended.

An attenuated virus vaccine for prevention of herpes zoster is FDA-approved for use in immunocompetent persons aged ≥50 years, but is recommended for use beginning at age 60 years by the Advisory Committee on Immunization Practices (ACIP). The zoster vaccine is contraindicated in persons with CD4 cell counts <200 cells/μL.

Special Considerations During Pregnancy

HIV-infected pregnant women who are susceptible to VZV and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 10 days)[22] after exposure to VZV **(AIII)**. If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV **(CIII)**. Pregnant women should not receive varicella vaccine **(AIII)**.

Specific risks among HIV-infected women with varicella during pregnancy have not been reported. For HIV-seronegative women with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when infection occurs at or before 12 weeks' gestation, 2.2% with infection at 13 to 20 weeks, and is negligible after 20 weeks.[38] Women with varicella during the first half of pregnancy should be counseled about the risks and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.[38] Administration of varicella-zoster immune globulin is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. Infants born to women who have varicella from 5 days before until 2 days after delivery should receive VariZIG to reduce the severity and mortality of neonatal varicella acquired by exposure to maternal viremia **(AIII)**.

Oral acyclovir or valacyclovir are the preferred treatments for HIV-infected pregnant women who have uncomplicated varicella during pregnancy **(BIII)**. Pregnant women who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) **(AII)**.

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated shingles in pregnant HIV-infected women is oral acyclovir or valacyclovir **(BIII)**. Pregnant women should not receive the herpes zoster vaccine **(AIII)**.

Recommendations for Preventing and Treating Varicella Zoster Virus (VZV) Infections (page 1 of 2)

Pre-Exposure Prevention of VZV Primary Infection

Indications:

- Adult and adolescent patients with CD4 count ≥200 cells/mm^3 without documentation of vaccination, health-care provider diagnosis or verification of a history of varicella or herpes zoster, laboratory confirmation of disease, or persons who are seronegative for VZV **(CIII)**

Note: Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended.

Vaccination:

- Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ) administered 3 months apart **(CIII)**
- If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)**.
- VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts **(BIII)**.
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination **(CIII)**.
- If post-exposure acyclovir has been administered, wait at least 3 days before varicella vaccine **(CIII)**.

Post-Exposure Prophylaxis:

*Indication **(AIII)**:*

- Close contact with a person who has active varicella or herpes zoster, *and*
- Is susceptible to VZV (i.e., has no history of vaccination or of either condition, or is known to be VZV seronegative)

Preferred Prophylaxis:

- VariZIG 125 international units per 10 kg (maximum of 625 international units) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster **(AIII)**
- VariZIG can be obtained only through an expanded access program under a treatment IND by contacting FFF Enterprise at (800) 843-7477.
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination **(CIII)**.

Note: Patients receiving monthly high dose IVIG (i.e., > 400 mg/kg) are likely to be protected against VZV and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before VZV exposure.

Alternative Prophylaxis (Begin 7–10 Days After Exposure):

- Acyclovir 800 mg PO 5 times/day for 5–7 days **(BIII)**, *or*
- Valacyclovir 1 g PO TID for 5–7 days **(BIII)**

Note:

- Neither these pre-emptive interventions nor post-exposure varicella vaccination have been studied in HIV-infected adults and adolescents.
- If acyclovir or valacyclovir is used, varicella vaccines should not be given until at least 72 hours after the last dose of the antiviral drug.

Treatment of Varicella Infections

Primary Varicella Infection (Chickenpox)

Uncomplicated Cases

Preferred Therapy:

- Valacyclovir 1 g PO TID **(AII)**, *or*
- Famciclovir 500 mg PO TID **(AII)**

Alternative Therapy:

- Acyclovir 800 mg PO 5 times daily **(BII)**

Duration:

- 5–7 days

Severe or Complicated Cases:

- Acyclovir 10–15 mg/kg IV q8h for 7–10 days **(AIII)**
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if no evidence of visceral involvement is evident **(BIII)**

Herpes Zoster (Shingles)

Acute Localized Dermatomal

Preferred Therapy:

- Valacyclovir 1000 mg PO TID **(AII)**, *or*
- Famciclovir 500 mg PO TID **(AII)**

Alternative Therapy:

- Acyclovir 800 mg PO 5 times daily **(BII)**

Duration:

- 7–10 days, longer duration should be considered if lesions resolve slowly

Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident **(AII)**
- Switch to oral therapy (valacyclovir 1 g TID, famciclovir 500 mg TID, or acyclovir 800 mg PO 5 times daily)—to complete a 10–14 day course, when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving **(BIII)**

PORN

- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Ganciclovir 5 mg/kg and/or foscarnet 90 mg/kg IV q12h ***plus*** ganciclovir 2 mg/0.05mL and/or foscarnet 1.2 mg/0.05mL intravitreal twice weekly **(AIII)**
- Optimize ART regimen **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with ophthalmologist.

Note: ganciclovir ocular implants are no longer commercially available

ARN

- Acyclovir 10 - 15 mg/kg IV q8h for 10–14 days, followed by valacyclovir 1 g PO TID for 6 weeks PLUS ganciclovir 2 mg/0.05mL intravitreal twice weekly X 1-2 doses **(AIII)**
- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with ophthalmologist.

Key to Acronyms: ARN = acute retinal necrosis; CD4 = CD4 T lymphocyte cell; IND = investigational new drug application; IV = intraveneously; IVIG = intraveneous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; q(n)h = every "n" hours; SQ = subcutaneously; TID = three times a day; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus

References

1. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis*. Nov 1992;166(5):1153-1156. Available at http://www.ncbi.nlm.nih.gov/pubmed/1308664.
2. Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984-1997. District of Columbia Gay Cohort Study. Multicenter Hemophilia Cohort Study. *J Infect Dis*. Dec 1999;180(6):1784-1789. Available at http://www.ncbi.nlm.nih.gov/pubmed/10558932.
3. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr*. Oct 1 2005;40(2):169-174. Available at http://www.ncbi.nlm.nih.gov/pubmed/16186734.
4. Vanhems P, Voisin L, Gayet-Ageron A, et al. The incidence of herpes zoster is less likely than other opportunistic infections to be reduced by highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. Jan 1 2005;38(1):111-113. Available at http://www.ncbi.nlm.nih.gov/pubmed/15608535.
5. Levin MJ, Anderson JP, Seage GR, 3rd, Williams PL. Short-term and long-term effects of highly active antiretroviral therapy on the incidence of herpes zoster in HIV-infected children. *J Acquir Immune Defic Syndr*. Feb 1 2009;50(2):182-191. Available at http://www.ncbi.nlm.nih.gov/pubmed/19131890.
6. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics*. Jan 2008;121(1):e150-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/18086820.
7. Wallace MR, Hooper DG, Pyne JM, Graves SJ, Malone JL. Varicella immunity and clinical disease in HIV-infected adults. *South Med J*. Jan 1994;87(1):74-76. Available at http://www.ncbi.nlm.nih.gov/pubmed/8284723.
8. Gnann JW, Jr., Crumpacker CS, Lalezari JP, et al. Sorivudine versus acyclovir for treatment of dermatomal herpes zoster in human immunodeficiency virus-infected patients: results from a randomized, controlled clinical trial. Collaborative Antiviral Study Group/AIDS Clinical Trials Group, Herpes Zoster Study Group. *Antimicrob Agents Chemother*. May 1998;42(5):1139-1145. Available at http://www.ncbi.nlm.nih.gov/pubmed/9593141.
9. Harrison RA, Soong S, Weiss HL, Gnann JW, Jr., Whitley RJ. A mixed model for factors predictive of pain in AIDS patients with herpes zoster. *J Pain Symptom Manage*. Jun 1999;17(6):410-417. Available at http://www.ncbi.nlm.nih.gov/pubmed/10388246.
10. Veenstra J, van Praag RM, Krol A, et al. Complications of varicella zoster virus reactivation in HIV-infected homosexual men. *AIDS*. Apr 1996;10(4):393-399. Available at http://www.ncbi.nlm.nih.gov/pubmed/8728043.
11. Engstrom RE, Jr., Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS. *Ophthalmology*. Sep 1994;101(9):1488-1502. Available at http://www.ncbi.nlm.nih.gov/pubmed/8090452.
12. Ormerod LD, Larkin JA, Margo CA, et al. Rapidly progressive herpetic retinal necrosis: a blinding disease characteristic of advanced AIDS. *Clin Infect Dis*. Jan 1998;26(1):34-45; discussion 46-37. Available at http://www.ncbi.nlm.nih.gov/pubmed/9455507.
13. Yin PD, Kurup SK, Fischer SH, et al. Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: successful management with intravitreal injections and monitoring with quantitative PCR. *J Clin Virol*. Mar 2007;38(3):254-259. Available at http://www.ncbi.nlm.nih.gov/pubmed/17280866.
14. Leung J, Harpaz R, Baughman AL, et al. Evaluation of laboratory methods for diagnosis of varicella. *Clin Infect Dis*. Jul 1 2010;51(1):23-32. Available at http://www.ncbi.nlm.nih.gov/pubmed/20504232.
15. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis*. Jul 15 2006;194(2):247-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/16779732.
16. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. Apr 2006;25(4):368-370. Available at http://www.ncbi.nlm.nih.gov/pubmed/16567993.
17. Bekker V, Westerlaken GH, Scherpbier H, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. *AIDS*. Nov 28 2006;20(18):2321-2329. Available at http://www.ncbi.nlm.nih.gov/pubmed/17117018.
18. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. *J Infect Dis*. Jun 15 2010;201(12):1806-1810. Available at http://www.ncbi.nlm.nih.gov/pubmed/20441519.

19. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. Jun 22 2007;56(RR-4):1-40. Available at http://www.ncbi.nlm.nih.gov/pubmed/17585291.

20. Centers for Disease Control and Prevention. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med*. Jan 5 2010;152(1):36-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/20048270.

21. Centers for Disease Control and Prevention. A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. *MMWR Morb Mortal Wkly Rep*. Mar 3 2006;55(8):209-210. Available at http://www.ncbi.nlm.nih.gov/pubmed/16511443.

22. Centers for Disease C, Prevention. FDA approval of an extended period for administering VariZIG for postexposure prophylaxis of varicella. *MMWR Morb Mortal Wkly Rep*. Mar 30 2012;61(12):212. Available at http://www.ncbi.nlm.nih.gov/pubmed/22456121.

23. American Academy of Pediatrics. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29 ed2002.

24. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children--a collaborative study. *J Pediatr*. Oct 1982;101(4):622-625. Available at http://www.ncbi.nlm.nih.gov/pubmed/6750068.

25. Arvin AM. Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis*. Jan 2002;13(1):12-21. Available at http://www.ncbi.nlm.nih.gov/pubmed/12118839.

26. Carcao MD, Lau RC, Gupta A, Huerter H, Koren G, King SM. Sequential use of intravenous and oral acyclovir in the therapy of varicella in immunocompromised children. *Pediatr Infect Dis J*. Jul 1998;17(7):626-631. Available at http://www.ncbi.nlm.nih.gov/pubmed/9686730.

27. Balfour HH, Jr., Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. Jun 16 1983;308(24):1448-1453. Available at http://www.ncbi.nlm.nih.gov/pubmed/6343861.

28. Scott IU, Luu KM, Davis JL. Intravitreal antivirals in the management of patients with acquired immunodeficiency syndrome with progressive outer retinal necrosis. *Archives of ophthalmology*. Sep 2002;120(9):1219-1222. Available at http://www.ncbi.nlm.nih.gov/pubmed/12215102.

29. Moorthy RS, Weinberg DV, Teich SA, et al. Management of varicella zoster virus retinitis in AIDS. *The British journal of ophthalmology*. Mar 1997;81(3):189-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/9135381.

30. Austin RB. Progressive outer retinal necrosis syndrome: a comprehensive review of its clinical presentation, relationship to immune system status, and management. *Clin Eye Vis Care*. Dec 2000;12(3-4):119-129. Available at http://www.ncbi.nlm.nih.gov/pubmed/11137426.

31. Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. *Archives of ophthalmology*. Jun 2012;130(6):700-706. Available at http://www.ncbi.nlm.nih.gov/pubmed/22801826.

32. Kim SJ, Equi R, Belair ML, Fine HF, Dunn JP. Long-term preservation of vision in progressive outer retinal necrosis treated with combination antiviral drugs and highly active antiretroviral therapy. *Ocular immunology and inflammation*. Nov-Dec 2007;15(6):425-427. Available at http://www.ncbi.nlm.nih.gov/pubmed/18085485.

33. Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis*. Dec 1998;27(6):1510-1513. Available at http://www.ncbi.nlm.nih.gov/pubmed/9868668.

34. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med*. Jun 1 2001;110(8):605-609. Available at http://www.ncbi.nlm.nih.gov/pubmed/11382367.

35. Dunic I, Djurkovic-Djakovic O, Vesic S, Zerjav S, Jevtovic D. Herpes zoster as an immune restoration disease in AIDS patients during therapy including protease inhibitors. *Int J STD AIDS*. Jul 2005;16(7):475-478. Available at http://www.ncbi.nlm.nih.gov/pubmed/16004625.

36. Espinosa E, Pena-Jimenez A, Ormsby CE, Vega-Barrientos R, Reyes-Teran G. Later onset of herpes zoster-associated immune reconstitution inflammatory syndrome. *HIV Med*. Aug 2009;10(7):454-457. Available at http://www.ncbi.nlm.nih.gov/pubmed/19490175.

37. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis*. Dec 1998;27(6):1525-1527. Available at http://www.ncbi.nlm.nih.gov/pubmed/9868672.

38. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med*. Mar 31 1994;330(13):901-905. Available at http://www.ncbi.nlm.nih.gov/pubmed/8114861.

Human Herpesvirus-8 Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Human herpesvirus-8 (HHV-8) seroprevalence among the general population in the United States is 1% to 5%. The seroprevalence is greater among men who have sex with men (20%–77%),[1] regardless of HIV infection, and is also higher in certain Mediterranean countries (10%–20%) and in parts of sub-Saharan Africa (30%–80%).[2] HHV-8 is etiologically associated with all forms of Kaposi's sarcoma ([KS] i.e., classic, endemic, transplant-related, and AIDS-related) and certain rare neoplastic disorders (such as primary effusion lymphoma) and lymphoproliferative disorders (multicentric Castleman's disease) The precise pathogenesis is unclear even though seroconversion to HHV-8 precedes the development of these tumors.[3] Patients who are HHV-8 seropositive and have HHV-8 viremia have an increased risk (approximately nine-fold) for developing KS compared with HHV-8 seropositive men without HHV-8 viremia.[4] HHV-8 viremia almost always accompanies symptomatic episodes of multicentric Castleman's disease.[5]

The overall prevalence of KS was as high as 30% among patients with AIDS before the advent of effective antriretroviral therapy (ART).[6] The incidence of KS, which increased nearly 10-fold in the United States between 1981 and 1987, began to gradually decline in 1987.[7] Reasons for this reduction in KS incidence prior to the widespread availability of ART are likely to be multiple, including the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by HIV-infected individuals of antiviral drugs that may have activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).[8] Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.[9-12] A more marked reduction in KS incidence occurred in 1996, shortly after the introduction of protease inhibitor-containing ART in the United States. Today the incidence of KS in the United States remains approximately 3-fold higher than before the HIV pandemic, and notably KS incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[13] Primary effusion cell lymphoma and multicentric Castleman's disease remain rare.[14]

KS and primary effusion lymphoma are described most frequently among HIV-infected persons with more advanced immunosuppression (CD4 T lymphocyte [CD4] cell counts <200 cells/μL), although they can occur at any CD4 cell count. Multicentric Castleman's disease can present at any CD4 cell count. Recent reports of KS occurring at higher CD4 cell counts in the United States[15,16] suggest that clinicians caring for patients with HIV should be vigilant for the clinical manifestations of KS in patients at risk of HHV-8 infection, regardless of CD4 cell count.

Clinical Manifestations

Most individuals with chronic HHV-8 infection are asymptomatic.[17] Acquisition of HHV-8 in immunocompetent children and organ transplant recipients has been associated with a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.[18,19] KS manifestations vary widely, but most patients have nontender, purplish, indurated skin lesions. Intraoral lesions are common and visceral dissemination can occur, occasionally without the presence of skin lesions. Multicentric Castleman's disease manifests with generalized adenopathy and fever and can progress to multi-organ failure.[14] Primary effusion lymphoma characteristically presents with effusions of the pleural, pericardial, or abdominal spaces; mass lesions can be seen but are less common manifestations.

Diagnosis

The diagnoses of KS, multicentric Castlemans disease and primary effusion lymphoma depend on cytologic and immunologic cell markers, as well as histology. Routine screening for HHV-8 by polymerese chain

reaction (PCR) or serologic testing for HHV-8 antibody is not indicated for HIV-infected persons. Use of PCR to quantify HHV-8 in the peripheral blood has no established role in the diagnosis of KS, multicentric Castleman's disease and primary effusion lymphoma.[5]

Preventing Exposure

Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions.[1,17,20] Viral shedding may result in HHV-8 transmission to uninfected partners through behaviors associated with exposure to saliva or genital secretions. Recommendations related to preventing exposure to HHV-8 do not exist; screening patients for HHV-8 serostatus and recommending behavioral modifications based on such information is not likely to be highly effective, has not been validated, and **is not currently recommended (CIII)**.

Preventing Disease

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of KS, the toxicity of current anti-HHV-8 therapy outweighs the potential benefits of administration **(BIII)**. Because the strongest risk factor for the development of KS in HIV-positive individuals is a low CD4 cell count,[21] early initiation of ART is likely to be the most effective measure for the prevention of KS.

Treating Disease

Although ganciclovir, foscarnet, and cidofovir have *in vitro* activity against HHV-8 and limited studies indicate these agents may be associated with reduced KS disease progression or lesion regression, larger and more definitive studies are needed to determine whether antiviral therapy has a useful role in managing HHV-8-associated diseases. KS regression has been documented after ganciclovir or foscarnet therapy, although one study indicated cidofovir was ineffective.[22]

The use of IV ganciclovir or oral valganciclovir is an option for treatment of multicentric Castleman's disease **(CII)**. A 3-week course of twice-daily IV ganciclovir or oral valganciclovir was associated with remissions in multicentric Castleman's disease in one report,[23] and a combination of valganciclovir and high-dose zidovudine given for 7 to 21 days led to durable clinical remissions of the disease **(CII)**.[24] Rituximab also is an effective alternative to antiviral therapy in the treatment of multicentric Castleman's disease **(CII)**,[25,26] though up to one-third of patients treated with rituximab may have subsequent exacerbations or emergence of KS.[27,28]

Chemotherapy, in combination with ART, should be administered to patients with primary effusion cell lymphoma or visceral KS **(AI)** and is likely to be a useful adjunctive therapy in individuals with widely disseminated cutaneous KS **(BIII)**. Some clinicians recommend valganciclovir as adjunctive therapy in the treatment of primary effusion lymphoma but there are no convincing data that it is useful **(CIII)**.[29,30]

Detailed recommendations for treatment of HHV-8 malignancies (including chemotherapy and radiation therapy) are beyond the scope of these guidelines. Treatment should be undertaken in consultation with an experienced specialist **(AIII)**.

Special Considerations When Starting ART

Early initiation of ART is likely to prevent incident KS and primary effusion cell lymphoma, though no studies have confirmed this hypothesis to date. ART that suppresses HIV replication should be administered to all HIV-infected patients with KS, primary effusion cell lymphoma, or multicentric Castleman's disease **(AII)**, although insufficient evidence exists to support using one ART regimen over another.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Immune reconstitution inflammatory syndrome (IRIS) has been a reported complication among HHV-8-

infected patients initiating ART.

KS: In one series, new onset KS or exacerbations of previously stable disease were the most common IRIS syndrome in a cohort of HIV-infected patients in Seattle.[31] Over half of Ugandan patients with mild-to-moderate KS experienced an exacerbation when initating ART.[32] Reliable predictors of KS-IRIS have not been identified.

Multicentric Castleman's disease: A small number of patients with HIV-associated multicentric Castleman's disease were also observed to have a clinical decompensation upon initiation of ART.[33,34]

Primary effusion lymphoma: No data exist on the frequency with which initiation of ART complicates the course of primary effusion lymphoma.

Taken together, it is clear that neither the incidence nor predictors of HHV-8-associated IRIS are well-described, but suppression of HIV replication and immune reconstitution are key components of therapy and initiation of ART should not be delayed **(AIII)**.

Preventing Recurrence

Effective suppression of HIV replication with ART in HIV-infected patients with KS may prevent KS progression or occurrence of new lesions, and because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS **(AII)**. Suppression of HIV replication also is recommended for patients with multicentric Castleman's disease **(AIII)** and those with malignant lymphoproliferative disorders **(AIII)**.

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among HIV-infected pregnant women varies by geographic area, ranging from 1.7% among U.S.-born and 3.6% among Haitian-born women in New York City to 11.6% among pregnant women from 4 other U.S. cities.[35] Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,[36] although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.[37] HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for HIV-infected pregnant women **(AIII)**. Antiviral therapy for HHV-8 infection in pregnancy **is not recommended** **(AIII)**.

In vitro models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting.[38-41]

Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,[42,43] higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),[44] and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.[45] Data indicate increased mortality through age 24 months among HIV-infected infants born to HHV-8-seropositive compared with HHV-8-seronegative mothers,[42-44,46-51] but these studies could not completely account for other confounding factors affecting HIV-infected infants. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive compared with HHV-8 antibody-negative women.[46-51]

Recommendations for Treating HHV-8 Diseases—Kaposi Sarcoma (KS), Primary Effusion Lymphoma (PEL), Multicentric Castleman's Disease (MCD)

Mild-to-Moderate KS:

- Initiation or optimization of ART **(AII)**

Advanced KS:

- Chemotherapy (in consultation with specialist) + ART [visceral KS **(AI)** or widely disseminated KS **(BIII)**]

PEL:

- Chemotherapy (in consultation with specialist) + ART **(AI)**
- Oral valganciclovir or IV ganciclovir might be used as adjunctive therapy **(CIII)**

MCD:

Preferred Therapy (in consultation with a specialist):

- Valganciclovir 900 mg PO BID **(CII)** for 3 weeks, *or*
- Ganciclovir 5 mg/kg IV q12h **(CII)** for 3 weeks, *or*
- Valganciclovir 900 mg PO BID + zidovudine 600 mg PO q6h for 7–21 days **(CII)**

Alternative Therapy for MCD:

- Rituximab 375 mg/m^2 given weekly for 4–8 weeks, may be an alternative to, or used adjunctively with, antiviral therapy **(CII)**

Other Considerations:

- Patients who received rituximab for treatment of MCD may experience subsequent exacerbation or emergence of KS

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intraveneously; KS = Karposi Sarcoma; MCD = multicentric Castleman's disease; PEL = primary effusion lymphoma; PO = orally; q(n)h = every "n" hours

References

1. Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med*. Nov 9 2000;343(19):1369-1377. Available at http://www.ncbi.nlm.nih.gov/pubmed/11070101.
2. Dollard SC, Butler LM, Jones AMG, et al. Substantial regional differences in human herpesvirus 8 seroprevalence in sub-Saharan Africa: Insights on the origin of the "Kaposi's sarcoma belt". *International Journal of Cancer*. 2010;127(10):2395-2401. Available at http://dx.doi.org/10.1002/ijc.25235.
3. Gao SJ, Kingsley L, Hoover DR, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med.* Jul 25 1996;335(4):233-241. Available at http://www.ncbi.nlm.nih.gov/pubmed/8657239.
4. Lennette ET, Blackbourn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. *Lancet*. Sep 28 1996;348(9031):858-861. Available at http://www.ncbi.nlm.nih.gov/pubmed/8826812.
5. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood*. Sep 15 2000;96(6):2069-2073. Available at http://www.ncbi.nlm.nih.gov/pubmed/10979949.
6. Beral V. The epidemiology of cancer in AIDS patients. *AIDS*. 1991;5 Suppl 2:S99-103. Available at http://www.ncbi.nlm.nih.gov/pubmed/1845066.
7. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst*. Aug 21 2002;94(16):1204-1210. Available at http://www.ncbi.nlm.nih.gov/pubmed/12189223.
8. Casper C. Defining a role for antiviral drugs in the treatment of persons with HHV-8 infection. *Herpes: the journal of the IHMF*. Aug 2006;13(2):42-47. Available at http://www.ncbi.nlm.nih.gov/pubmed/16895654.
9. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with

cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. *N Engl J Med*. Apr 8 1999;340(14):1063-1070. Available at http://www.ncbi.nlm.nih.gov/pubmed/10194235.

10. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis*. Aug 1998;178(2):349-359. Available at http://www.ncbi.nlm.nih.gov/pubmed/9697714.
11. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. *AIDS*. Sep 1996;10(10):1101-1105. Available at http://www.ncbi.nlm.nih.gov/pubmed/8874626.
12. Glesby MJ, Hoover DR, Weng S, et al. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the Multicenter AIDS Cohort Study. *J Infect Dis*. Jun 1996;173(6):1477-1480. Available at http://www.ncbi.nlm.nih.gov/pubmed/8648224.
13. Casper C. The increasing burden of HIV-associated malignancies in resource-limited regions. *Annual review of medicine*. 2011;62:157-170. Available at http://www.ncbi.nlm.nih.gov/pubmed/20868276.
14. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *British journal of haematology*. Apr 2005;129(1):3-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/15801951.
15. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. *N Engl J Med*. Sep 27 2007;357(13):1352-1353. Available at http://www.ncbi.nlm.nih.gov/pubmed/17898112.
16. Mani D, Neil N, Israel R, Aboulafia DM. A retrospective analysis of AIDS-associated Kaposi's sarcoma in patients with undetectable HIV viral loads and CD4 counts greater than 300 cells/mm^3. *J Int Assoc Physicians AIDS Care (Chic)*. Sep-Oct 2009;8(5):279-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/19721098.
17. Casper C, Krantz E, Selke S, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. *J Infect Dis*. Jan 1 2007;195(1):30-36. Available at http://www.ncbi.nlm.nih.gov/pubmed/17152006.
18. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpesvirus 8 infection in immunocompetent children. *JAMA*. Mar 13 2002;287(10):1295-1300. Available at http://www.ncbi.nlm.nih.gov/pubmed/11886321.
19. Luppi M, Barozzi P, Schulz TF, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. *N Engl J Med*. Nov 9 2000;343(19):1378-1385. Available at http://www.ncbi.nlm.nih.gov/pubmed/11070102.
20. Casper C, Redman M, Huang ML, et al. HIV infection and human herpesvirus-8 oral shedding among men who have sex with men. *J Acquir Immune Defic Syndr*. Mar 1 2004;35(3):233-238. Available at http://www.ncbi.nlm.nih.gov/pubmed/15076237.
21. Lodi S, Guiguet M, Costagliola D, et al. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. *J Natl Cancer Inst*. Jun 2 2010;102(11):784-792. Available at http://www.ncbi.nlm.nih.gov/pubmed/20442214.
22. Little RF, Merced-Galindez F, Staskus K, et al. A pilot study of cidofovir in patients with kaposi sarcoma. *J Infect Dis*. Jan 1 2003;187(1):149-153. Available at http://www.ncbi.nlm.nih.gov/pubmed/12508160.
23. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood*. Mar 1 2004;103(5):1632-1634. Available at http://www.ncbi.nlm.nih.gov/pubmed/14615380.
24. Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood*. Jun 30 2011;117(26):6977-6986. Available at http://www.ncbi.nlm.nih.gov/pubmed/21487108.
25. Bower M, Newsom-Davis T, Naresh K, et al. Clinical Features and Outcome in HIV-Associated Multicentric Castleman's Disease. *J Clin Oncol*. Jun 20 2011;29(18):2481-2486. Available at http://www.ncbi.nlm.nih.gov/pubmed/21555697.
26. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman disease. *Blood*. Oct 15 2003;102(8):2786-2788. Available at http://www.ncbi.nlm.nih.gov/pubmed/12842986.
27. Gerard L, Berezne A, Galicier L, et al. Prospective Study of Rituximab in Chemotherapy-Dependent Human

Immunodeficiency Virus Associated Multicentric Castleman's Disease: ANRS 117 CastlemaB Trial. *J Clin Oncol*. August 1, 2007 2007;25(22):3350-3356. Available at http://jco.ascopubs.org/cgi/content/abstract/25/22/3350.

28. Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med*. Dec 18 2007;147(12):836-839. Available at http://www.ncbi.nlm.nih.gov/pubmed/18087054.
29. Aboulafia DM. Interleukin-2, ganciclovir, and high-dose zidovudine for the treatment of AIDS-associated primary central nervous system lymphoma. *Clin Infect Dis*. Jun 15 2002;34(12):1660-1662. Available at http://www.ncbi.nlm.nih.gov/pubmed/12032910.
30. Crum-Cianflone NF, Wallace MR, Looney D. Successful secondary prophylaxis for primary effusion lymphoma with human herpesvirus 8 therapy. *AIDS*. Jul 13 2006;20(11):1567-1569. Available at http://www.ncbi.nlm.nih.gov/pubmed/16847420.
31. Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. *Clin Infect Dis*. Feb 1 2012;54(3):424-433. Available at http://www.ncbi.nlm.nih.gov/pubmed/22095568.
32. Martin D, Gutkind JS. Kaposi's sarcoma virally encoded, G-protein-coupled receptor: a paradigm for paracrine transformation. *Methods Enzymol*. 2009;460:125-150. Available at http://www.ncbi.nlm.nih.gov/pubmed/19446723.
33. Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive Castleman disease in human immunodeficiency virus-infected patients: the impact of highly active antiretroviral therapy. *Clin Infect Dis*. Oct 1 2002;35(7):880-882. Available at http://www.ncbi.nlm.nih.gov/pubmed/12228826.
34. Achenbach C, Kitahata MM. Recurrence or Worsening of AIDS-defining Opportunistic Infection (OI) due to Immune Reconstitution Inflammatory Syndrome (IRIS) During Initial HAART Among a Clinic-Based Population. Paper presented at: 48th ICAAC/IDSA 46th Annual Meeting; October 25-28, 2008; Washington, DC.
35. Goedert JJ, Kedes DH, Ganem D. Antibodies to human herpesvirus 8 in women and infants born in Haiti and the USA. *Lancet*. May 10 1997;349(9062):1368. Available at http://www.ncbi.nlm.nih.gov/pubmed/9149705.
36. Huang LM, Huang SY, Chen MY, et al. Geographical differences in human herpesvirus 8 seroepidemiology: a survey of 1,201 individuals in Asia. *J Med Virol*. Mar 2000;60(3):290-293. Available at http://www.ncbi.nlm.nih.gov/pubmed/10630961.
37. Lisco A, Barbierato M, Fiore JR, et al. Pregnancy and human herpesvirus 8 reactivation in human immunodeficiency virus type 1-infected women. *J Clin Microbiol*. Nov 2006;44(11):3863-3871. Available at http://www.ncbi.nlm.nih.gov/pubmed/16943357.
38. Berger P, Dirnhofer S. Kaposi's sarcoma in pregnant women. *Nature*. Sep 7 1995;377(6544):21-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/7659155.
39. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. *Nature*. May 4 1995;375(6526):64-68. Available at http://www.ncbi.nlm.nih.gov/pubmed/7723844.
40. Rabkin CS, Chibwe G, Muyunda K, Musaba E. Kaposi's sarcoma in pregnant women. *Nature*. Sep 7 1995;377(6544):21; author reply 22. Available at http://www.ncbi.nlm.nih.gov/pubmed/7659154.
41. Schulz TF, Weiss RA. Kaposi's sarcoma. A finger on the culprit. *Nature*. Jan 5 1995;373(6509):17-18. Available at http://www.ncbi.nlm.nih.gov/pubmed/7800029.
42. Gutierrez-Ortega P, Hierro-Orozco S, Sanchez-Cisneros R, Montano LF. Kaposi's sarcoma in a 6-day-old infant with human immunodeficiency virus. *Archives of dermatology*. Mar 1989;125(3):432-433. Available at http://www.ncbi.nlm.nih.gov/pubmed/2923454.
43. McCarthy GA, Kampmann B, Novelli V, Miller RF, Mercey DE, Gibb D. Vertical transmission of Kaposi's sarcoma. *Archives of disease in childhood*. May 1996;74(5):455-457. Available at http://www.ncbi.nlm.nih.gov/pubmed/8669966.
44. Sitas F, Newton R, Boshoff C. Increasing probability of mother-to-child transmission of HHV-8 with increasing maternal antibody titer for HHV-8. *N Engl J Med*. Jun 17 1999;340(24):1923. Available at http://www.ncbi.nlm.nih.gov/pubmed/10375309.
45. Mbulaiteye S, Marshall V, Bagni RK, et al. Molecular evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus in Uganda and K1 gene evolution within the host. *J Infect Dis*. May 1 2006;193(9):1250-1257.

Available at http://www.ncbi.nlm.nih.gov/pubmed/16586362.

46. Mantina H, Kankasa C, Klaskala W, et al. Vertical transmission of Kaposi's sarcoma-associated herpesvirus. *Int J Cancer*. Dec 1 2001;94(5):749-752. Available at http://www.ncbi.nlm.nih.gov/pubmed/11745472.
47. Serraino D, Locatelli M, Songini M, et al. Human herpes virus-8 infection among pregnant women and their children: results from the Sardinia-IDDM Study 2. *Int J Cancer*. Mar 1 2001;91(5):740-741. Available at http://www.ncbi.nlm.nih.gov/pubmed/11267990.
48. Gessain A, Mauclere P, van Beveren M, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. *Int J Cancer*. Apr 12 1999;81(2):189-192. Available at http://www.ncbi.nlm.nih.gov/pubmed/10188717.
49. Bourboulia D, Whitby D, Boshoff C, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. *JAMA*. Jul 1 1998;280(1):31-32. Available at http://www.ncbi.nlm.nih.gov/pubmed/9660357.
50. Whitby D, Smith NA, Matthews S, et al. Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women. *J Infect Dis*. Jan 1999;179(1):234-236. Available at http://www.ncbi.nlm.nih.gov/pubmed/9841845.
51. Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet*. Sep 23 2000;356(9235):1062-1065. Available at http://www.ncbi.nlm.nih.gov/pubmed/11009141.

Human Papillomavirus Disease (Last updated February 3, 2016; last reviewed September 24, 2015)

Epidemiology

Human papillomavirus (HPV) infection is the major risk factor for development of cervical cancer,[1,2] the fourth most common cancer in women worldwide.[3,4] Nearly all cervical cancers test positive for HPV genetic sequences,[5-7] most notably the E6 and E7 oncogenes,[8-10] which are thought to play a major role in immortalization of cervical epithelial cells.[11]

Cervical infection with HPV is common and occurs primarily through sexual transmission.[12-16] Penetrative sexual intercourse is not strictly necessary for HPV transmission,[17] but it is the primary risk factor for HPV infection, and HPV prevalence is low in young women who report only non-penetrative sexual contact.[17,18] The vast majority of cervical HPV infections resolve or become latent and undetectable, but in a subset of women, infection persists.[12,19,20] Persistence of oncogenic HPV infection is a necessary step in HPV-related cervical tumorigenesis,[1,21,22] although it appears insufficient for final cell transformation.[11] At least 12 HPV types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[22-24] HPV68 is considered "probably oncogenic," and several others are considered "possibly oncogenic." HPV16 alone, though, accounts for approximately 50% of cervical cancers in the general population and HPV18 for another 10% to 15%. The other oncogenic HPV types each individually account for fewer than 5% of tumors. HPV types 6 and 11 cause 90% of genital warts, but are not considered oncogenic.[22-24]

In the United States and Western Europe, women with HIV/AIDS have significantly higher rates of cervical cancer than women in the general population,[25-31] and recent cohort data show a direct relationship between low CD4 T lymphocyte (CD4) cell count and cervical cancer risk.[32] In Africa, the data are more limited and inconsistent,[33] but prospective registry-based study found increased risk of cervical cancer in women with HIV/AIDS.[34] HIV infection and low CD4 cell count also have been consistently and strongly associated with HPV infection itself and with precancerous cervical lesions, including low-grade cervical intraepithelial neoplasia (CIN), and the precursor to cervical cancer, CIN 3.[35-47] Higher rates of HPV infection and CIN are seen in adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.[36,48,49] Brogly and colleagues reported that 30% of female adolescents infected with HIV during the perinatal period had an abnormality (e.g., atypical squamous cells of uncertain significance [ASC-US] or greater) on their first Pap test; genital warts were also common in this group, with a cumulative rate of 12% by age 19.

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.[1,23,50-52] HPV16 is the type present in most HPV-positive non-cervical cancers.[1,23,50,53,54] Patients with HIV/AIDS also have significantly elevated incidence of these tumors relative to the general population,[25,55,56] and CD4 cell count has been related to risk of anal cancer.[32] Furthermore, high-grade anal intraepithelial neoplasia (AIN), the likely anal cancer precursor lesion, is more common in HIV-seropositive adults and adolescents than in HIV-seronegative adults and adolescents,[57-59] as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).[60-62]

Despite the associations between HIV and CD4 cell count with HPV-related cancers and precancers, the impact of antiretroviral therapy (ART) on the incidence of HPV-related tumors is uncertain, and it is possible that the impact differs by tumor type. Some studies found decreased persistence/progression of CIN with ART,[63] including a study that distinguished between adherence and non-adherence to ART.[64] Incidence of cervical cancer itself, however, has not changed significantly since ART was introduced,[55] but anal cancer incidence appears to have increased.[55] Use of ART did not affect CIN rates in adolescents with perinatally or horizontally acquired HIV.[36,49] The incidence of high-grade VIN was not reduced with ART use, even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART,[60] and some[65,66] but not other[67,68] studies reported increased rates of oral warts following ART initiation. The burden of HPV-related cancers can be expected to increase in HIV-seropositive patients, given successful prolongation of life with

use of ART for HIV suppression, potentially longer duration of HPV persistence, and accumulation of somatic mutations and epigenetic changes that contribute to carcinogenesis. This clinical scenario may be of particular concern for HPV-related cancers, such as anal cancers, that are not currently subject to routine screening. However, increasing use of HPV vaccination in adolescents and young adults may begin to reduce the risk of HPV-associated cancers in HIV-infected persons in later life.

Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; anogenital squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers are also caused by HPV.[69]

Oral, genital (condyloma acuminata), and anal warts are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions may measure a few millimeters to 1 to 2 cm in diameter. Most warts are asymptomatic, but warts can be associated with itching or discomfort. In cases associated with more severe immunosuppression, marked enlargement may cause dyspareunia or dyschezia. Lesions of any size may cause cosmetic concerns.

Intraepithelial neoplasias (CIN, VIN, VAIN, and AIN) are often asymptomatic but may manifest with bleeding or itching. Related cancers may also be asymptomatic or may manifest with bleeding, pain, odor, or a visible/ palpable mass. External lesions may be visible or palpable. Similarly, squamous cell cancers at these sites also can be asymptomatic or may manifest with bleeding, pain, or a visible/palpable mass.

Diagnosis

Warts/Condyloma

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy, although biopsy is needed only if the diagnosis is uncertain, the lesions do not respond to standard therapy, or warts are pigmented, indurated, fixed, bleeding, or ulcerated. No data support the use of HPV testing for screening, diagnosis or management of visible genital/oral warts or oral HPV disease in HIV-infected patients.[70]

Cervical Neoplasia

The same cytology (Pap test), and colposcopic techniques with biopsy are used to detect CIN among HIV-seronegative and HIV-seropositive patients (see section on Preventing Disease). At the time of cytology screening, the genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia, or invasive cancer.

Anal and Vulvar/Vaginal Neoplasia

AIN, VAIN, and VIN are recognized through visual inspection, including high-resolution anoscopy, colposcopy, and biopsy as needed. A digital examination of the anal canal to feel for masses should be performed as part of routine evaluation.

Cervical Cancer Screening Recommendations

Available HPV tests can detect up to 14 oncogenic HPV types in clinical specimens and are sensitive for the detection of cervical cancer precursors.[71-73] Some commercially available HPV tests will specify whether the oncogenic HPV includes genotypes HPV16 or HPV16/18. The available tests for oncogenic HPV have been incorporated into the screening algorithms. **Note:** HPV testing is always for oncogenic HPV types only; there is no role in testing for non-oncogenic HPV.

Possible Pap test results include:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL (low-grade squamous intraepithelial lesion) or CIN1 (cervical intraepithelial neoplasia grade 1)

- HSIL (high-grade squamous intraepithelial lesion) or CIN2, 3 (cervical intraepithelial neoplasia grade 2,3)
- ASCUS (Atypical squamous cells of undetermined significance)
- ASC-H (Atypical squamous cells, cannot rule out a high grade lesion)
- AGC (Atypical glandular cells)

HIV-Infected Women Aged <30 years

Screening

The Pap test is the primary mode for cervical cancer screening for HIV-infected women <30 years. Screening for these women should commence within 1 year of the onset of sexual activity regardless of mode of HIV transmission (e.g., sexual activity, perinatal exposure) but no later than 21 years old. HIV-infected women 21 to 29 years old should have a Pap test at the time of initial diagnosis with HIV. Provided the initial Pap test for young (or newly diagnosed) HIV-infected woman is normal, the next Pap test should be in 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 consecutive Pap tests are normal, follow up Pap tests should be every 3 years **(BII)**. Co-testing (Pap test and HPV test) is not recommended for HIV-infected women <30 years of age.

Abnormal Pap Test Results

For ASC-US Pap test, if reflex HPV testing is positive, a referral to colposcopy is recommended. If HPV testing is not available or not done, then repeat cytology in 6 to 12 months is recommended **(AII)**. For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended **(AII)**.

For LSIL or worse (including ASC-H, AGC and HSIL) referral to colposcopy is recommended (regardless of reflex HPV result, if done).

Rationale

These recommendations reflect evidence that HIV-infected women <21 years of age and sexually active may have a high rate of progression of abnormal cytology[36] **(BII)**. No similar prospective data are available for adolescents infected during the perinatal period, but as noted earlier, Brogly and colleagues reported that 30% of such adolescents had ASC-US or greater on their first cervical Pap test.[49] The mean age at the time of the first Pap test was 16.7 years, with a range of 13 to 23 years.

Because of the relatively high HPV prevalence before age 30, HPV co-testing is not recommended for HIV-uninfected women in this age group.

HIV-Infected Women Aged ≥30 years

Cervical cancer screening in HIV-infected women should continue throughout a woman's lifetime (and not, as in the general population, end at 65 years of age). Either Pap testing only or Pap testing and HPV co-testing is acceptable for screening.

Pap Testing Only

If screening with Pap tests alone, the HIV-infected woman should have a Pap test at the time of HIV-diagnosis (baseline), then every 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 consecutive Pap tests are normal, follow-up Pap tests should be every 3 years **(BII)**.

Pap and HPV Co-Testing

If co-testing with Pap and HPV is available, then co-testing can be done at the time of diagnosis or age 30. **(BII)**. Co-test negative women (i.e., a normal Pap and negative HPV test) can have their next cervical cancer screening in 3 years.

Those who are Pap test normal but positive for HPV should have repeat co-testing in one year (unless genotype testing for 16 or 16/18 is positive). If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

If the initial HPV results identify HPV16 or HPV16/18, then referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV 16/18 is negative, then repeat co-testing in one year is recommended. If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

Abnormal Pap Test Results

For ASC-US Pap test, if reflex HPV testing is positive, then referral to colposcopy is recommended. If HPV testing is not available, repeat cytology in 6 to 12 months is recommended **(AII)**. For any result ≥ ASC-US on repeat cytology, referral to colposcopy is recommended **(AII)**.

For LSIL or worse (including ASC-H, AGC and HSIL) referral to colposcopy is recommended (regardless of HPV result, if done).

Rationale

Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force allow for use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow for a prolonged cervical cancer screening interval in HIV-infected women who are older than age 29 and have normal cervical cytology with concurrent negative HPV testing.[74,75]

Preventing HPV Infection

HPV Vaccine

There are three FDA-approved HPV vaccines: bivalent, quadrivalent, and 9-valent. All three vaccines prevent HPV16 and HPV18 infections and prevent pre-cancers (and likely cancers) caused by HPV types 16 and 18. The quadrivalent and 9-valent HPV vaccines also prevent HPV6 and HPV11 infections and genital warts due to these types. The 9-valent vaccine also prevents infection and precancers due to 5 additional types, HPV 31, 33, 45, 52, and 58.

Clinical trials of all three vaccines have demonstrated high efficacy for prevention of cervical precancer due to vaccine types in women.[76-78] Clinical trials of the quadrivalent HPV vaccine have also demonstrated high efficacy for prevention of vaginal and vulvar precancer in women. The quadrivalent vaccine has been shown to prevent anal HPV6/11/16/18 infections, AIN and external genital lesions related to these types.[79-82] Although there are no efficacy data with the 9-valent HPV vaccine in men, a clinical trial established the safety of the vaccine in young men aged 16 to 26 and showed similar antibody concentrations as a young women aged 16 to 26 in whom efficacy was established.[83] The CDC Advisory Committee on Immunization Practices has recommended routine vaccination with any HPV vaccines for 11- or 12-year-old girls.[84,85] The vaccine series can be started at age 9. Catch-up vaccination is recommended for 13- to 26-year-old females who have not been vaccinated **(AI)**. All 3 HPV vaccines should be delivered through a series of 3 intramuscular injections over a 6-month period. The second and third doses should be given at 1 to 2 months and then 6 months after the first dose. The Advisory Committee also recommended routine quadrivalent or 9-valent HPV vaccination of males aged 11 to 12 years in the general population, with catch-up vaccination up to age 21 **(AI)**. Vaccination was also recommended for males aged 22 to 26 years who are immunocompromised, MSM, or who test positive for HIV infection.[84,86]

No studies have been completed on the efficacy of HPV vaccination against infections or related disease in HIV-infected individuals. However, several studies have been completed on the safety and immunogenicity of the bivalent and quadrivalent vaccines[87,88] in HIV-infected individuals.

The studies have demonstrated that these vaccine are safe and immunogenic in a broad range of HIV-infected groups. No data are available on the safety and immunogenicity of the 9-valent vaccine in HIV-infected populations. Some studies demonstrated antibody levels lower in HIV-infected individuals compared to those who are uninfected, however, the clinical significance of this observation is unknown.

A randomized clinical trial of quadrivalent HPV vaccine found the vaccine to be safe and immunogenic in HIV-infected children aged >7 to <12 years;[87] albeit type-specific antibody levels were less for HPV 6 and 18 compared to age-matched historic HIV-uninfected controls.[87] A long term follow-up study of these children found the vaccine to be safe and immunogenic in children aged 7 to 12 years; after 72 weeks, ≥94% had antibodies to HPV 6, 11, and 16, but only 76% had antibodies to HPV18.[89] In this study, after a fourth dose, all children demonstrated an anamnestic response to all HPV vaccine types. A study of the quadrivalent HPV vaccine in HIV-infected males aged 21 to 67 years found the vaccine to be immunogenic to all 4 HPV types and well tolerated.[88] A study of the quadrivalent HPV vaccine in HIV-infected females aged 13 to 45 years (mean age 36) found the vaccine to be immunogenic to all 4 HPV types. However, seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL compared with ≤200 cells/μL.[90] In a study of the bivalent HPV vaccine comparing antibody response in HIV-infected and HIV-uninfected females aged 18 to 25 years[91] all subjects seroconverted to HPV16 and 18 and the vaccine was well tolerated but geometric mean titers were lower in the HIV-infected females compared with those who were HIV-uninfected.

The 9-valent HPV vaccine targets more HPV types associated with cancer than bivalent or quadrivalent HPV vaccines. The additional 5 high-risk HPV types covered by the 9-valent vaccine were found in 4.2% to 18.3% of HPV-associated anogenital cancers depending on location in U.S. men and women.[92] Overall, 4% of HPV associated cancers in males and 14% of HPV associated cancers in females in the US are estimated to be due to these additional 5 types.

HPV vaccination is recommended for HIV-infected girls and boys aged 9 through 12 years **(AIII)**. Ongoing studies are evaluating the efficacy and duration of immune response in HIV-infected boys and girls. Because the HPV vaccines work to prevent initial HPV infection, administration ideally should precede sexual exposure to HPV. Because some HIV-infected individuals have had many sex partners prior to vaccination, the vaccines may be of less benefit in these patients than in those with few or no lifetime sex partners. Current data from HIV-infected individuals aged 13 to 26 years on prior exposure to HPV types included in currently available vaccines are insufficient to determine the proportion that would benefit from vaccination. Given existing evidence that the vaccine is safe and immunogenic,[87,88] and because of the potential benefit in preventing HPV-associated disease and cancer in this population, HPV vaccination is recommended for HIV-infected males and females aged 13 through 26 **(BIII)**.

Vaccination is likely to be less effective in HIV-infected men and women aged 19 to 26 than in those who are younger because of the strong possibility that they have already acquired HPV vaccine types through sexual activity. Some experts recommend basing vaccination on a discussion between the patient and health care provider that includes the likelihood of previous HPV exposure and potential benefit of the vaccine **(CIII)**. Data are insufficient to recommend vaccination for those older than age 26, and neither vaccine is approved for use in men or women older than age 26. HIV-infected women who have been vaccinated should also have routine cervical cancer screening because the vaccine does not prevent all HPV types that may be precursors to cervical cancer and because the vaccine may be less effective in HIV-infected women (especially those with low CD4 cell counts) than in HIV-uninfected women.

Condom Use

The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as preventing HIV and other sexually transmitted diseases (STDs) **(AII)**. Latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV.[93] Consistent and proper use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among

women.18 Similarly, recent cross-sectional data suggested that among heterosexual men, consistent condom use was associated with 50% lower odds of HPV infection of the penis.[94] A meta-analysis found that condom use was associated with reduced risk of genital warts, and in women, with lower rates of CIN.[95] A randomized clinical trial of condom use in heterosexual couples found significantly more frequent clearance of CIN and HPV among women randomized to condom use, and of penile lesions among their male partners.[96,97] In HIV-infected women, several studies have observed lower rates of HPV detection associated with use of condoms.[35,98]

Male condoms have benefits in reducing risk of transmission of nearly all STDs[99] (including HIV infection) during heterosexual intercourse and same-sex intercourse between men. In circumstances when a male condom cannot be used properly, a female condom (e.g., an FC1 or FC2 Female Condom®) should be considered for heterosexual vaginal intercourse **(AII)** and for heterosexual or male same-sex anal intercourse **(BIII)**.[100-103] Data on FC1 and FC2 Female Condoms suggest the devices are protective against STDs.[102]

Male Circumcision

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from randomized clinical trials[104-107] and observational studies.[108-113] Observational studies in the general population also suggest that circumcision is associated with lower risk of penile cancer,[114-117] and of cervical cancer in sexual partners.[118] Relevant data in HIV-seropositive men, however, are limited,[106] and the findings to date suggest that, while protective, the effects of circumcision against HPV infection may be less in HIV-infected than in HIV-seronegative individuals.[106,107] Furthermore, no clinical trials have assessed whether circumcision of HIV-seropositive men reduces risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners. Evidence is insufficient to recommend adult male circumcision solely for the purpose of reducing the risk of oncogenic HPV infection in HIV-infected men, or their sex partners, in the United States.

Preventing Disease

Preventing Vaginal and Vulvar Cancer

Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for HIV-seropositive women **(AIII)**. However, women with a history of high-grade CIN, adenocarcinoma in situ, or invasive cervical cancer are at increased risk and should be followed with an annual vaginal cuff Pap test **(BIII)**.[119,120] For patients with an abnormal vaginal cuff Pap test results with no visible vaginal colposcopic abnormalities, the use of Lugol's iodine to stain the vagina is recommended **(AIII)**. Vaginal colposcopy also is indicated in the presence of concomitant cervical and vulvar lesions.[121,122] Classification of VAIN parallels that of the cervix, that is, VAIN 1, VAIN 2, and VAIN 3.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

Preventing Anal Cancer

Some cost-effectiveness evaluations indicate that in HIV-seropositive patients, screening for lesions using anal cytology and treating anal precancerous lesions to reduce risk of anal cancer in HIV-infected patients may provide clinical benefits comparable to measures for prevention of other opportunistic infection.[123-125] AIN lesions are similar in many ways to CIN, but there may be differences in natural history, optimal screening, and treatment approaches to prevent cancer. At this time, no national recommendations exist for routine screening for anal cancer.[70] However, some specialists recommend anal cytologic screening or high resolution anoscopy[125] for HIV-seropositive men and women **(CIII)**. An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer **(BIII)**.[126] Screening for anal cancer with anal cytology should not be done without the availability of referral for high resolution anoscopy. If anal cytology is performed and indicates ASC-US, then ASC cannot rule out ASC-H, LSIL, or high-grade

squamous intraepithelial lesion (HSIL), then it should be followed by high-resolution anoscopy **(BIII)**. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer **(BIII)** (see section on treatment for details on treating AIN).

Treating Disease

Preferred and Alternative Approaches for Treatment, Including Duration of Therapy

Treating Genital and Oral Warts

HIV-infected patients may have larger or more numerous warts, may not respond as well to therapy for genital warts as individuals who are immunocompetent, and may have more frequent recurrences after treatment.[61,127,128] Genital warts are not life-threatening, and they may regress without therapy, even in patients with HIV, especially when immunity is relatively preserved. Treatments are available for genital warts but none is uniformly effective or uniformly preferred.[70] Lacking randomized clinical trials (RCTs) specific to HIV-infected individuals, guidelines for treatment of STDs in HIV-infected patients should be followed.[70] More than one treatment option may be required for refractory or recurrent lesions in patients with HIV infection. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-grade disease. Intra-anal, vaginal, or cervical warts should be treated and managed by a specialist.

Patient-applied treatments are generally recommended for uncomplicated external warts that can be easily identified and treated by the patient. Imiquimod (5% cream), is a topical cytokine inducer that should be applied at bedtime on 3 non-consecutive nights per week, for up to 16 weeks, until lesions are no longer visible. The treatment area should be washed with soap and water 6 to 10 hours after the application **(BII)**. Podofilox 0.5% solution or gel should be applied to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times **(BIII)**. Another option is sinecatechins (15% ointment), a topical botanical product that contains active catechins from green tea and should be applied 3 times daily for up to 16 weeks, until warts are completely cleared and not visible **(BIII)**.

No clinical trials of this latter treatment option have been conducted in HIV-infected individuals.

Provider-applied treatments such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery, are typically recommended for complex or multicentric lesions, lesions inaccessible to patient-applied therapy, or because of patient or provider preference.

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis and should be applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists recommend allowing the lesion to thaw and freezing a second time in each session **(BIII)**.

TCA and BCA (80% to 90%) each act as caustic agents to destroy wart tissue and should be applied to warts only and allowed to dry until a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible **(BIII)**.

Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts **(BIII)**. Laser surgery is an option, but is usually more expensive **(CIII)**.

Topical application of cidofovir has reported activity against genital warts **(CIII)**, but no topical formulation is commercially available. Intralesional interferon has been used for the treatment of genital warts but because of cost, difficulty of administration, and potential for systemic side effects such as fever, fatigue, myalgias, and leukopenia, it is not recommended for first-line treatment **(CIII)**. Podophyllin resin may be an alternative provider-applied treatment, with strict adherence to recommendations on application. It has inconsistent potency in topical preparations, and can have toxicity that may limit routine use in clinical practice.

There is no consensus on optimal treatments of oral warts. Many treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgery is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.[129]

Treating CIN and Cervical Cancer

HIV-infected women with CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in HIV-infected women should be managed according to ASCCP guidelines.[130]

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (i.e., cryotherapy, laser vaporization, electrocautery, diathermy, and cold coagulation) or excisional methods (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization), whereas women with unsatisfactory colposcopy should be treated only with excisional methods **(AII)**. In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended **(AII)**. Hysterectomy is acceptable for treatment of recurrent or persistent biopsy-confirmed high-grade CIN **(BII)**; if invasive disease is suspected, the patient should be managed in consultation with a gynecologic oncologist. For HIV-infected adolescents, the ASCCP guidelines for adolescents and young women should continue to be followed. In these patients, progression of lesions is more common, and so is recurrence. Therefore, close observation, as outlined in the guidelines, should be considered for management of CIN 1, CIN 2, CIN2,3 not otherwise specified, and histologic HSIL in HIV-infected adolescents and women younger than 25 **(BIII)**. If compliance is questionable, then it may be preferable to follow the treatment arm of management for CIN 2, CIN2, 3, and HSIL **(BIII)**.

Management of invasive cervical, vaginal, and vulvar cancer should follow National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Although complication and failure rates may be higher in HIV-infected women, standard treatment appears safe and efficacious.

Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed as for vulvovaginal warts. Treatment of high-grade VIN/VAIN should be individualized in consultation with a specialist and is dependent upon the patient's medical condition and the location and extent of the disease. Various treatment modalities are available for VIN, including local excision, laser vaporization, ablation, and imiquimod therapy. Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO2 laser, and excisional procedures with electrosurgical loops or a scalpel excision.

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

Treating AIN and Anal Cancer

For AIN2-3, no adequate RCTs have been reported and data are insufficient to recommend a specific treatment approach. A RCT was recently initiated to determine if treatment of AIN2-3 reduces the incidence of anal cancer in HIV-infected patients. Definitive guidelines on anal screening and treatment in HIV-infected patients will likely follow from the results of this study. Until then, treatment decisions are based on assessment of the size and location of the lesion and its histologic grade. **All treatment modalities are associated with high rates of recurrence.** Topical treatment options including 5-FU, cidofovir,[131] intra-anal imiquimod, and provider-applied TCA have demonstrated moderate efficacy for treatment of intra-anal AIN.[132] Ablative therapies including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfrecator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3.

In a retrospective analysis, infrared coagulation was proven to have moderate efficacy in treatment of AIN2

or 3 in HIV-seropositive patients[133] and it was safe and well tolerated in this population in a prospective AIDS Malignancy Consortium study.[134] No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

The most commonly used treatment for anal cancer is combination radiation and chemotherapy.

Treating HPV-Associated Disease at Other Sites, Including the Penis and Mouth

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ between HIV-infected and HIV-uninfected men and women. Data suggest a more favorable prognosis for HPV-associated oropharyngeal cancers, compared with non-HPV-associated oropharyngeal cancers.[135]

Special Considerations With Regard To Starting ART

Currently, there are no data to indicate that decisions about initiation of ART should be influenced by presence of HPV-related oral, anal, or genital disease. Some studies have found decreased persistence or progression of CIN during ART,[63] including the only study that distinguished adherent from nonadherent ART use.[64] However, the incidence of cervical cancer itself has not changed significantly since the introduction of ART,[55] and anal cancer incidence appears to have increased.[55] Use of ART did not affect rates of CIN in adolescents with perinatally or horizontally acquired HIV.[36,49] Similarly, use of ART was not associated with a reduced incidence of high-grade vulvar neoplasia but it was associated with lower rates of low-grade vulvar lesions and anal or genital warts.[136] Some,[65,66] but not all, studies[67,68] reported increased rates of oral warts following ART initiation. Study results do not indicate that treatment for CIN or AIN should be modified for patients receiving ART. Conversely, no evidence indicates that ART should be instituted or modified solely for the purpose of treating CIN or AIN, and the diagnosis of CIN or AIN in HIV-infected individuals should not be considered an indication for initiation of ART.

Monitoring Response to Therapy and Adverse Events (Including IRIS)

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments.

Because recurrences of CIN and cervical cancer after conventional therapy are more common in patients who are HIV-seropositive, they should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines **(AII)** (see Preventing Disease and Treating sections).[130,137,138] Treatment of CIN with ablative and excisional modalities can be associated with several adverse events, such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis; individualized treatment of adverse events is required.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and in rare cases, development of abscesses, fissures, or fistulas. Patients can be monitored for adverse events using the methods previously described.

Treatment for anal cancer with combination radiation and chemotherapy is associated with a high rate of morbidity, even when the treatment is successful. The most important complication is radiation-associated proctitis.

Managing Treatment Failure

For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered **(AIII)**. Biopsy should be considered to exclude VIN. Genital warts often require more than one course of treatment.

Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to ASCCP guidelines.[130]

There is no consensus on the treatment of biopsy-proven recurrent VIN and surgical excision can be considered.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines.[130] In one study of HIV-infected women treated for high-grade CIN, low-dose intravaginal 5-FU (2 g twice weekly for 6 months) reduced the short-term risk of recurrence.[139] Clinical experience with this therapy, however, is too limited to provide a recommendation for use and no follow-up study to confirm these observations has been reported. No guidelines exist regarding frequency of monitoring after therapy for VIN, but twice-yearly vulvar inspection appears reasonable for women who have been treated for VIN. Women who have been treated for high-grade VAIN should be managed like those with CIN2, that is, with cytology at 6 and 12 months after therapy, and annually thereafter.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

Special Considerations during Pregnancy

HIV-infected pregnant women with genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (such as an ob/gyn and an infectious disease physician). Pregnancy may be associated with an increased frequency and rate of growth of genital warts.[140-142] Podofilox should not be used during pregnancy **(BIII)**. At present, the evidence is insufficient to recommend imiquimod use during pregnancy **(CIII)**. No anomalies have been observed with the use of imiquimod in animals during pregnancy. There have been several case series describing the use of imiquimod during pregnancy also without any significant adverse effects.[143-145]

Other topical treatments (such as BCA and TCA) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy **(AIII)**. Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of early-onset recurrent respiratory papillomatosis in children. This condition is rare but is more common among children of women who have genital warts at delivery.[146] Cesarean delivery is not known to prevent this condition in infants and children.[140-142,147] No change in obstetrical management is indicated for women with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding **(AIII)**.[148-151]

Pregnant women should undergo cervical cancer screening as recommended above for non-pregnant women. Cytobrush sampling can be done during pregnancy.[152] Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer **(BIII)**. Increased bleeding may occur with cervical biopsy during pregnancy. Endocervical curettage is contraindicated in pregnant women **(AIII)**.

Pregnant women with ASC-US can be managed the same as non-pregnant women, although deferral of colposcopy until at least 6 weeks postpartum is recommended **(CIII)**. Treatment of CIN is not recommended during pregnancy unless invasive disease is suspected. Pregnant women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and development of a delivery plan. Vaginal delivery is not recommended for women with invasive cervical cancer.

For women without suspicion of invasive disease, re-evaluation with cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy **(CIII)**. However, in a combined analysis of 5 RCTs of the HPV6/11/16/18 vaccine, administration of the vaccine to women who became pregnant during the course of the trial did not appear to negatively affect pregnancy outcomes.[153]

The effects of treatment of AIN on pregnancy are unknown. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

Recommendations for Cervical Cancer Screening for HIV-Infected Women

HIV-Infected Women Aged <30 Years:

- If younger than age 21, known to be HIV-infected or newly diagnosed with HIV, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- HIV-infected women aged 21–29 should have a Pap test following initial diagnosis.
- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30.

HIV-Infected Women Aged >30 Years

Pap Testing Only:

- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**.
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.

Or:

Pap Test and HPV Co-Testing:

- Pap test and HPV co-testing should be done at baseline **(BII)**.
- If result of the Pap test is normal and HPV co-testing is negative, follow up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the result of the Pap test is normal but HPV co-testing is positive, follow up test with Pap test and HPV co-testing should be performed in one year.
- If the one year follow-up Pap test is abnormal or HPV co-testing is positive, referral to colposcopy is recommended.

Preventing First Episode of HPV Infection

Indications for HPV Vaccination:

- HIV-infected; aged 9–26 years **(BIII)**

Note: Please refer to Pediatric OI guidelines for vaccination of boys and girls younger than age 13.

Vaccination Schedules

For Women:

- HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine bivalent (Types 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**

For Men:

- HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**

Recommendations for Preventing Human Papillomavirus Infections

Treating Condyloma Acuminata (Genital Warts)

Note: HIV-infected patients may have larger or more numerous warts, may not respond as well to therapy for genital warts, and have a higher risk of recurrence after treatment than HIV-negative individuals. More than one treatment option maybe required for refractory or recurrent lesions. Intra-anal, vaginal, or cervical warts should be treated and managed by a specialist.

Patient-Applied Therapy

For Uncomplicated External Warts that can be Easily Identified and Treated by the Patient:

- Imiquimod 5% cream: Apply to lesions at bedtime on 3 non-consecutive nights a week and wash the treatment area with soap and water 6–10 hours after application **(BII)**, repeating the cycle until lesions are no longer seen, for up to 16 weeks, *or*
- Sinecatechins 15% ointment: Apply to area 3 times daily for up to 16 weeks, until warts are not visible **(BIII)**.

Provider-Applied Therapy

For Complex or Multicentric Lesions, Lesions Inaccessible to Patient-Applied Treatments, or Patient/Provider Preference:

- Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen; repeat every 1–2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists allow the lesion to thaw, and then freeze a second time in each session **(BIII)**.
- TCA or BCA cauterization: 80% to 90% aqueous solution, apply to warts only and allow the area to dry until a white frost develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. Repeat treatment weekly for up to 6 weeks until lesions are no longer visible **(BIII)**.
- Surgical excision **(BIII)** or laser surgery **(CIII)** can be performed for external or anal warts.

Key to Acronyms: BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; OI = opportunistic infection; TCA = trichloroacetic acid

References

1. World Health Organization International Agency for Research on Cancer. Volume 90: Human Papillomaviruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. 2007.
2. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. Sep 8 2007;370(9590):890-907. Available at http://www.ncbi.nlm.nih.gov/pubmed/17826171.
3. American Cancer Society. Global Cancer Facts & Figures 3rd Edition. Atlanta, GA. 2015.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. Dec 15 2010;127(12):2893-2917. Available at http://www.ncbi.nlm.nih.gov/pubmed/21351269.
5. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst*. Jun 7 1995;87(11):796-802. Available at http://www.ncbi.nlm.nih.gov/pubmed/7791229.
6. Wheeler CM, Hunt WC, Joste NE, Key CR, Quint WG, Castle PE. Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst*. Apr 1 2009;101(7):475-487. Available at http://www.ncbi.nlm.nih.gov/pubmed/19318628.
7. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. Feb 6 2003;348(6):518-527. Available at http://www.ncbi.nlm.nih.gov/pubmed/12571259.
8. Kraus I, Molden T, Holm R, et al. Presence of E6 and E7 mRNA from human papillomavirus types 16, 18, 31, 33, and 45 in the majority of cervical carcinomas. *J Clin Microbiol*. Apr 2006;44(4):1310-1317. Available at http://www.ncbi.nlm.nih.gov/pubmed/16597856.
9. Castle PE, Dockter J, Giachetti C, et al. A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer. *Clin Cancer Res*. May 1 2007;13(9):2599-2605. Available at http://www.ncbi.nlm.nih.gov/pubmed/17473189.
10. Ratnam S, Coutlee F, Fontaine D, et al. Clinical performance of the PreTect HPV-Proofer E6/E7 mRNA assay in comparison with that of the Hybrid Capture 2 test for identification of women at risk of cervical cancer. *J Clin Microbiol*. Aug 2010;48(8):2779-2785. Available at http://www.ncbi.nlm.nih.gov/pubmed/20573862.

11. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond)*. May 2006;110(5):525-541. Available at http://www.ncbi.nlm.nih.gov/pubmed/16597322.

12. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. Feb 12 1998;338(7):423-428. Available at http://www.ncbi.nlm.nih.gov/pubmed/9459645.

13. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. *J Infect Dis*. Jan 15 2008;197(2):279-282. Available at http://www.ncbi.nlm.nih.gov/pubmed/18179386.

14. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis*. Sep-Oct 1993;20(5):274-278. Available at http://www.ncbi.nlm.nih.gov/pubmed/8235925.

15. Wheeler CM, Parmenter CA, Hunt WC, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. *Sex Transm Dis*. Sep-Oct 1993;20(5):286-289. Available at http://www.ncbi.nlm.nih.gov/pubmed/8235927.

16. Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. *J Infect Dis*. Oct 1996;174(4):679-689. Available at http://www.ncbi.nlm.nih.gov/pubmed/8843203.

17. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. Feb 1 2003;157(3):218-226. Available at http://www.ncbi.nlm.nih.gov/pubmed/12543621.

18. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. Jun 22 2006;354(25):2645-2654. Available at http://www.ncbi.nlm.nih.gov/pubmed/16790697.

19. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr*. Feb 1998;132(2):277-284. Available at http://www.ncbi.nlm.nih.gov/pubmed/9506641.

20. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis*. Apr 1995;171(4):1026-1030. Available at http://www.ncbi.nlm.nih.gov/pubmed/7706782.

21. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. Mar 3 2010;102(5):315-324. Available at http://www.ncbi.nlm.nih.gov/pubmed/20157096.

22. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009;4:8. Available at http://www.ncbi.nlm.nih.gov/pubmed/19486508.

23. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. Apr 2009;10(4):321-322. Available at http://www.ncbi.nlm.nih.gov/pubmed/19350698.

24. Castle PE. The evolving definition of carcinogenic human papillomavirus. *Infect Agent Cancer*. 2009;4:7. Available at http://www.ncbi.nlm.nih.gov/pubmed/19432962.

25. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*. Sep 20 2000;92(18):1500-1510. Available at http://www.ncbi.nlm.nih.gov/pubmed/10995805.

26. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with *AIDS*. *J Natl Cancer Inst*. Aug 19 2009;101(16):1120-1130. Available at http://www.ncbi.nlm.nih.gov/pubmed/19648510.

27. Simard EP, Engels EA. Cancer as a cause of death among people with *AIDS* in the United States. *Clin Infect Dis*. Oct 15 2010;51(8):957-962. Available at http://www.ncbi.nlm.nih.gov/pubmed/20825305.

28. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*. Mar 16 2005;97(6):425-432. Available at http://www.ncbi.nlm.nih.gov/pubmed/15770006.

29. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/*AIDS* compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. Jul 7 2007;370(9581):59-67. Available at

http://www.ncbi.nlm.nih.gov/pubmed/17617273.

30. Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with *AIDS* in Italy in the HAART era. *Br J Cancer*. Mar 10 2009;100(5):840-847. Available at http://www.ncbi.nlm.nih.gov/pubmed/19223894.
31. Polesel J, Franceschi S, Suligoi B, et al. Cancer incidence in people with *AIDS* in Italy. *Int J Cancer*. Sep 1 2010;127(6):1437-1445. Available at http://www.ncbi.nlm.nih.gov/pubmed/20049835.
32. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. Dec 2009;10(12):1152-1159. Available at http://www.ncbi.nlm.nih.gov/pubmed/19818686.
33. Orem J, Otieno MW, Remick SC. *AIDS*-associated cancer in developing nations. *Curr Opin Oncol*. Sep 2004;16(5):468-476. Available at http://www.ncbi.nlm.nih.gov/pubmed/15314517.
34. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda *AIDS*-Cancer Registry Match Study. *Int J Cancer*. Feb 15 2006;118(4):985-990. Available at http://www.ncbi.nlm.nih.gov/pubmed/16106415.
35. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. Apr 20 2005;97(8):577-586. Available at http://www.ncbi.nlm.nih.gov/pubmed/15840880.
36. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. *J Infect Dis*. Oct 15 2004;190(8):1413-1421. Available at http://www.ncbi.nlm.nih.gov/pubmed/15378433.
37. Schrager LK, Friedland GH, Maude D, et al. Cervical and vaginal squamous cell abnormalities in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1989;2(6):570-575. Available at http://www.ncbi.nlm.nih.gov/pubmed/2555473.
38. Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol*. Sep 1990;38(3):377-382. Available at http://www.ncbi.nlm.nih.gov/pubmed/2227552.
39. Ahdieh L, Klein RS, Burk R, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. Sep 15 2001;184(6):682-690. Available at http://www.ncbi.nlm.nih.gov/pubmed/11517428.
40. Schuman P, Ohmit SE, Klein RS, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis*. Jul 1 2003;188(1):128-136. Available at http://www.ncbi.nlm.nih.gov/pubmed/12825181.
41. Massad LS, Riester KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr*. May 1 1999;21(1):33-41. Available at http://www.ncbi.nlm.nih.gov/pubmed/10235512.
42. Feingold AR, Vermund SH, Burk RD, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1990;3(9):896-903. Available at http://www.ncbi.nlm.nih.gov/pubmed/2166784.
43. Wright TC, Jr., Ellerbrock TV, Chiasson MA, Van Devanter N, Sun XW. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol*. Oct 1994;84(4):591-597. Available at http://www.ncbi.nlm.nih.gov/pubmed/8090399.
44. Sun XW, Ellerbrock TV, Lungu O, Chiasson MA, Bush TJ, Wright TC, Jr. Human papillomavirus infection in human immunodeficiency virus-seropositive women. *Obstet Gynecol*. May 1995;85(5 Pt 1):680-686. Available at http://www.ncbi.nlm.nih.gov/pubmed/7724095.
45. Heard I, Jeannel D, Bergeron C, Saada M, Henrion R, Kazatchkine MD. Lack of behavioural risk factors for squamous intraepithelial lesions (SIL) in HIV-infected women. *Int J STD AIDS*. Jun 1997;8(6):388-392. Available at http://www.ncbi.nlm.nih.gov/pubmed/9179650.
46. Delmas MC, Larsen C, van Benthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. *AIDS*. Aug 18 2000;14(12):1775-1784. Available at http://www.ncbi.nlm.nih.gov/pubmed/10985315.

47. Six C, Heard I, Bergeron C, et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS*. Jun 18 1998;12(9):1047-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/9662202.

48. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis*. Jul 1 2004;190(1):37-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/15195241.

49. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. *Am J Public Health*. Jun 2007;97(6):1047-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/17463385.

50. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine*. Aug 31 2006;24 Suppl 3:S3/11-25. Available at http://www.ncbi.nlm.nih.gov/pubmed/16949997.

51. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health*. Apr 2010;46(4 Suppl):S20-26. Available at http://www.ncbi.nlm.nih.gov/pubmed/20307840.

52. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. *Sex Health*. Sep 2010;7(3):244-252. Available at http://www.ncbi.nlm.nih.gov/pubmed/20719211.

53. Smith JS, Backes DM, Hoots BE, Kurman RJ, Pimenta JM. Human papillomavirus type-distribution in vulvar and vaginal cancers and their associated precursors. *Obstet Gynecol*. Apr 2009;113(4):917-924. Available at http://www.ncbi.nlm.nih.gov/pubmed/19305339.

54. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. Apr 1 2009;124(7):1626-1636. Available at http://www.ncbi.nlm.nih.gov/pubmed/19115209.

55. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. *Arch Intern Med*. Aug 9 2010;170(15):1337-1345. Available at http://www.ncbi.nlm.nih.gov/pubmed/20696958.

56. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer*. Jul 1 2008;123(1):187-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/18435450.

57. Wilkin TJ, Palmer S, Brudney KF, Chiasson MA, Wright TC. Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. *J Infect Dis*. Nov 1 2004;190(9):1685-1691. Available at http://www.ncbi.nlm.nih.gov/pubmed/15478076.

58. Kreuter A, Brockmeyer NH, Hochdorfer B, et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. *J Am Acad Dermatol*. Apr 2005;52(4):603-608. Available at http://www.ncbi.nlm.nih.gov/pubmed/15793509.

59. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS*. Sep 2 2005;19(13):1407-1414. Available at http://www.ncbi.nlm.nih.gov/pubmed/16103772.

60. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. Am J *Obstet Gynecol*. May 2004;190(5):1241-1248. Available at http://www.ncbi.nlm.nih.gov/pubmed/15167825.

61. Conley LJ, Ellerbrock TV, Bush TJ, Chiasson MA, Sawo D, Wright TC. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. *Lancet*. Jan 12 2002;359(9301):108-113. Available at http://www.ncbi.nlm.nih.gov/pubmed/11809252.

62. Jamieson DJ, Paramsothy P, Cu-Uvin S, Duerr A, Group HIVERS. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. *Obstet Gynecol*. May 2006;107(5):1023-1028. Available at http://www.ncbi.nlm.nih.gov/pubmed/16648406.

63. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. Jul 21 2004;96(14):1070-1076. Available at http://www.ncbi.nlm.nih.gov/pubmed/15265968.

64. Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Infect Dis*. Mar 2010;201(5):681-690. Available at http://www.ncbi.nlm.nih.gov/pubmed/20105077.

65. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papillomavirus-associated oral

warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. *Clin Infect Dis*. Mar 1 2002;34(5):641-648. Available at http://www.ncbi.nlm.nih.gov/pubmed/11803508.

66. Greenspan D, Canchola AJ, MacPhail LA, Cheikh B, Greenspan JS. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet*. May 5 2001;357(9266):1411-1412. Available at http://www.ncbi.nlm.nih.gov/pubmed/11356441.
67. Greenspan D, Gange SJ, Phelan JA, et al. Incidence of oral lesions in HIV-1-infected women: reduction with HAART. *J Dent Res*. Feb 2004;83(2):145-150. Available at http://www.ncbi.nlm.nih.gov/pubmed/14742653.
68. Hamza OJ, Matee MI, Simon EN, et al. Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy [HAART] in Dar es Salaam, Tanzania. *BMC Oral Health*. 2006;6:12. Available at http://www.ncbi.nlm.nih.gov/pubmed/16916469.
69. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. May 10 2007;356(19):1944-1956. Available at http://www.ncbi.nlm.nih.gov/pubmed/17494927.
70. CDC. 2010 STD Treatment Guidelines. 2010. Available at http://www.cdc.gov/std/treatment/.
71. Food and Drug Administration. Product approval information—licensing action, package insert. hc2 High-Risk HPV DNA Test. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf/P890064S009c.pdf. Accessed September 21, 2015.
72. Food and Drug Administration. Product approval information—licensing action, package insert. Cervista™ HPV HR test. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080014c.pdf. Accessed September 21, 2015.
73. Food and Drug Administration. Product approval information—licensing action, package insert. Cervista™ 16/18 test. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080015c.pdf. Accessed September 21, 2015.
74. Keller MJ, Burk RD, Xie X, et al. Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of oncogenic HPV infection. *JAMA*. Jul 25 2012;308(4):362-369. Available at http://www.ncbi.nlm.nih.gov/pubmed/22820789.
75. Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA*. Mar 23 2005;293(12):1471-1476. Available at http://www.ncbi.nlm.nih.gov/pubmed/15784870.
76. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. Jul 25 2009;374(9686):301-314. Available at http://www.ncbi.nlm.nih.gov/pubmed/19586656.
77. Group FIS. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. May 10 2007;356(19):1915-1927. Available at http://www.ncbi.nlm.nih.gov/pubmed/17494925.
78. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. Feb 19 2015;372(8):711-723. Available at http://www.ncbi.nlm.nih.gov/pubmed/25693011.
79. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. Oct 27 2011;365(17):1576-1585. Available at http://www.ncbi.nlm.nih.gov/pubmed/22029979.
80. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med*. Feb 3 2011;364(5):401-411. Available at http://www.ncbi.nlm.nih.gov/pubmed/21288094.
81. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet*. May 19 2007;369(9574):1693-1702. Available at http://www.ncbi.nlm.nih.gov/pubmed/17512854.
82. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. May 10 2007;356(19):1928-1943. Available at http://www.ncbi.nlm.nih.gov/pubmed/17494926.
83. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. Jul 2 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26144901.
84. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. Aug 29 2014;63(RR-05):1-30. Available at http://www.ncbi.nlm.nih.gov/pubmed/25167164.

85. Petrosky E, Bocchini JA, Jr., Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. Mar 27 2015;64(11):300-304. Available at http://www.ncbi.nlm.nih.gov/pubmed/25811679.

86. Centers for Disease C, Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. Dec 23 2011;60(50):1705-1708. Available at http://www.ncbi.nlm.nih.gov/pubmed/22189893.

87. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. Oct 2010;55(2):197-204. Available at http://www.ncbi.nlm.nih.gov/pubmed/20574412.

88. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. Oct 15 2010;202(8):1246-1253. Available at http://www.ncbi.nlm.nih.gov/pubmed/20812850.

89. Weinberg A, Song LY, Saah A, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. *J Infect Dis*. Oct 2012;206(8):1309-1318. Available at http://www.ncbi.nlm.nih.gov/pubmed/22859825.

90. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. Jul 1 2014;59(1):127-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/24723284.

91. Kahn JA, Xu J, Kapogiannis BG, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. *Clin Infect Dis*. Sep 2013;57(5):735-744. Available at http://www.ncbi.nlm.nih.gov/pubmed/23667266.

92. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. Jun 2015;107(6):djv086. Available at http://www.ncbi.nlm.nih.gov/pubmed/25925419.

93. Kish LS, McMahon JT, Bergfeld WF, Pelachyk JM. An ancient method and a modern scourge: the condom as a barrier against herpes. *J Am Acad Dermatol*. Nov 1983;9(5):769-770. Available at http://www.ncbi.nlm.nih.gov/pubmed/6685737.

94. Nielson CM, Harris RB, Nyitray AG, Dunne EF, Stone KM, Giuliano AR. Consistent condom use is associated with lower prevalence of human papillomavirus infection in men. *J Infect Dis*. Aug 15 2010;202(3):445-451. Available at http://www.ncbi.nlm.nih.gov/pubmed/20569156.

95. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis*. Nov 2002;29(11):725-735. Available at http://www.ncbi.nlm.nih.gov/pubmed/12438912.

96. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *Int J Cancer*. Dec 10 2003;107(5):811-816. Available at http://www.ncbi.nlm.nih.gov/pubmed/14566832.

97. Bleeker MC, Hogewoning CJ, Voorhorst FJ, et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. *Int J Cancer*. Dec 10 2003;107(5):804-810. Available at http://www.ncbi.nlm.nih.gov/pubmed/14566831.

98. Hankins C, Coutlee F, Lapointe N, et al. Prevalence of risk factors associated with human papillomavirus infection in women living with HIV. Canadian Women's HIV Study Group. *CMAJ*. Jan 26 1999;160(2):185-191. Available at http://www.ncbi.nlm.nih.gov/pubmed/9951439.

99. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. *Bull World Health Organ*. Jun 2004;82(6):454-461. Available at http://www.ncbi.nlm.nih.gov/pubmed/15356939.

100. Kelvin EA, Smith RA, Mantell JE, Stein ZA. Adding the female condom to the public health agenda on prevention of HIV and other sexually transmitted infections among men and women during anal intercourse. *Am J Public Health*. Jun 2009;99(6):985-987. Available at http://www.ncbi.nlm.nih.gov/pubmed/19372513.

101. Macaluso M, Blackwell R, Jamieson DJ, et al. Efficacy of the male latex condom and of the female polyurethane condom as barriers to semen during intercourse: a randomized clinical trial. *Am J Epidemiol*. Jul 1 2007;166(1):88-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/17420182.

102. French PP, Latka M, Gollub EL, Rogers C, Hoover DR, Stein ZA. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. *Sex Transm Dis*. May 2003;30(5):433-439. Available at http://www.ncbi.nlm.nih.gov/pubmed/12916135.

103. Waugh M. The role of condom use in sexually transmitted disease prevention: facts and controversies. *Clin Dermatol*. Sep-Oct 2010;28(5):549-552. Available at http://www.ncbi.nlm.nih.gov/pubmed/20797517.

104. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. *J Infect Dis*. Jan 1 2009;199(1):14-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/19086814.

105. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. Mar 26 2009;360(13):1298-1309. Available at http://www.ncbi.nlm.nih.gov/pubmed/19321868.

106. Serwadda D, Wawer MJ, Makumbi F, et al. Circumcision of HIV-infected men: effects on high-risk human papillomavirus infections in a randomized trial in Rakai, Uganda. *J Infect Dis*. May 15 2010;201(10):1463-1469. Available at http://www.ncbi.nlm.nih.gov/pubmed/20370481.

107. Gray RH, Serwadda D, Kong X, et al. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *J Infect Dis*. May 15 2010;201(10):1455-1462. Available at http://www.ncbi.nlm.nih.gov/pubmed/20370483.

108. Giuliano AR, Lazcano E, Villa LL, et al. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. *Int J Cancer*. Mar 15 2009;124(6):1251-1257. Available at http://www.ncbi.nlm.nih.gov/pubmed/19089913.

109. Lu B, Wu Y, Nielson CM, et al. Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. *J Infect Dis*. Feb 1 2009;199(3):362-371. Available at http://www.ncbi.nlm.nih.gov/pubmed/19133808.

110. Nielson CM, Schiaffino MK, Dunne EF, Salemi JL, Giuliano AR. Associations between male anogenital human papillomavirus infection and circumcision by anatomic site sampled and lifetime number of female sex partners. *J Infect Dis*. Jan 1 2009;199(1):7-13. Available at http://www.ncbi.nlm.nih.gov/pubmed/19086813.

111. Hernandez BY, Shvetsov YB, Goodman MT, et al. Reduced clearance of penile human papillomavirus infection in uncircumcised men. *J Infect Dis*. May 1 2010;201(9):1340-1343. Available at http://www.ncbi.nlm.nih.gov/pubmed/20350160.

112. Hernandez BY, Wilkens LR, Zhu X, et al. Circumcision and human papillomavirus infection in men: a site-specific comparison. *J Infect Dis*. Mar 15 2008;197(6):787-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/18284369.

113. Lajous M, Mueller N, Cruz-Valdez A, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. *Cancer Epidemiol Biomarkers Prev*. Jul 2005;14(7):1710-1716. Available at http://www.ncbi.nlm.nih.gov/pubmed/16030106.

114. Saibishkumar EP, Crook J, Sweet J. Neonatal circumcision and invasive squamous cell carcinoma of the penis: a report of 3 cases and a review of the literature. *Can Urol Assoc J*. Feb 2008;2(1):39-42. Available at http://www.ncbi.nlm.nih.gov/pubmed/18542727.

115. Schoen EJ, Oehrli M, Colby C, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. *Pediatrics*. Mar 2000;105(3):E36. Available at http://www.ncbi.nlm.nih.gov/pubmed/10699138.

116. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int J Cancer*. Sep 10 2005;116(4):606-616. Available at http://www.ncbi.nlm.nih.gov/pubmed/15825185.

117. Maden C, Sherman KJ, Beckmann AM, et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst*. Jan 6 1993;85(1):19-24. Available at http://www.ncbi.nlm.nih.gov/pubmed/8380060.

118. Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med*. Apr 11 2002;346(15):1105-1112. Available at http://www.ncbi.nlm.nih.gov/pubmed/11948269.

119. Kalogirou D, Antoniou G, Karakitsos P, Botsis D, Papadimitriou A, Giannikos L. Vaginal intraepithelial neoplasia (VAIN) following hysterectomy in patients treated for carcinoma in situ of the cervix. *Eur J Gynaecol Oncol*. 1997;18(3):188-191. Available at http://www.ncbi.nlm.nih.gov/pubmed/9174833.

120. Paramsothy P, Duerr A, Heilig CM, et al. Abnormal vaginal cytology in HIV-infected and at-risk women after hysterectomy. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):484-491. Available at http://www.ncbi.nlm.nih.gov/pubmed/15021313.

121. Petry KU, Kochel H, Bode U, et al. Human papillomavirus is associated with the frequent detection of warty and basaloid high-grade neoplasia of the vulva and cervical neoplasia among immunocompromised women. *Gynecol Oncol*. Jan 1996;60(1):30-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/8557224.

122. Chiasson MA, Ellerbrock TV, Bush TJ, Sun XW, Wright TC, Jr. Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with the human immunodeficiency virus. *Obstet Gynecol*. May 1997;89(5 Pt 1):690-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/9166302.

123. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA*. May 19 1999;281(19):1822-1829. Available at http://www.ncbi.nlm.nih.gov/pubmed/10340370.

124. Tatti S, Suzuki V, Fleider L, Maldonado V, Caruso R, Tinnirello Mde L. Anal intraepithelial lesions in women with human papillomavirus-related disease. *J Low Genit Tract Dis*. Oct 2012;16(4):454-459. Available at http://www.ncbi.nlm.nih.gov/pubmed/22968054.

125. Mallari AO, Schwartz TM, Luque AE, Polashenski PS, Rauh SM, Corales RB. Anal cancer screening in HIV-infected patients: is it time to screen them all? *Dis Colon Rectum*. Dec 2012;55(12):1244-1250. Available at http://www.ncbi.nlm.nih.gov/pubmed/23135582.

126. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. *Dermatol Ther*. Jan-Feb 2005;18(1):67-76. Available at http://www.ncbi.nlm.nih.gov/pubmed/15842614.

127. Silverberg MJ, Ahdieh L, Munoz A, et al. The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. *Sex Transm Dis*. Aug 2002;29(8):427-435. Available at http://www.ncbi.nlm.nih.gov/pubmed/12172526.

128. De Panfilis G, Melzani G, Mori G, Ghidini A, Graifemberghi S. Relapses after treatment of external genital warts are more frequent in HIV-positive patients than in HIV-negative controls. *Sex Transm Dis*. Mar 2002;29(3):121-125. Available at http://www.ncbi.nlm.nih.gov/pubmed/11875372.

129. Baccaglini L, Atkinson JC, Patton LL, Glick M, Ficarra G, Peterson DE. Management of oral lesions in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. Mar 2007;103 Suppl:S50 e51-23. Available at http://www.ncbi.nlm.nih.gov/pubmed/17379155.

130. Wright TC, Jr., Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. Oct 2007;197(4):346-355. Available at http://www.ncbi.nlm.nih.gov/pubmed/17904957.

131. Stier EA, Goldstone SE, Einstein MH, et al. Safety and efficacy of topical cidofovir to treat high-grade perianal and vulvar intraepithelial neoplasia in HIV-positive men and women. *AIDS*. Feb 20 2013;27(4):545-551. Available at http://www.ncbi.nlm.nih.gov/pubmed/23032420.

132. Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS*. Sep 24 2010;24(15):2331-2335. Available at http://www.ncbi.nlm.nih.gov/pubmed/20729710.

133. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum*. May 2005;48(5):1042-1054. Available at http://www.ncbi.nlm.nih.gov/pubmed/15868241.

134. Stier EA, Baranoski AS. Human papillomavirus-related diseases in HIV-infected individuals. *Curr Opin Oncol*. Sep 2008;20(5):541-546. Available at http://www.ncbi.nlm.nih.gov/pubmed/19106657.

135. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol*. Dec 20 2006;24(36):5630-5636. Available at http://www.ncbi.nlm.nih.gov/pubmed/17179101.

136. Massad LS, Schneider MF, Watts DH, et al. HPV testing for triage of HIV-infected women with papanicolaou smears read as atypical squamous cells of uncertain significance. *J Womens Health (Larchmt)*. Mar 2004;13(2):147-153. Available at http://www.ncbi.nlm.nih.gov/pubmed/15072728.

137. Wright TC, Jr., Koulos J, Schnoll F, et al. Cervical intraepithelial neoplasia in women infected with the human immunodeficiency virus: outcome after loop electrosurgical excision. *Gynecol Oncol*. Nov 1994;55(2):253-258. Available at http://www.ncbi.nlm.nih.gov/pubmed/7959293.

138. Fruchter RG, Maiman M, Sedlis A, Bartley L, Camilien L, Arrastia CD. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstet Gynecol*. Mar 1996;87(3):338-344. Available at http://www.ncbi.nlm.nih.gov/pubmed/8598951.

139. Maiman M, Watts DH, Andersen J, Clax P, Merino M, Kendall MA. Vaginal 5-fluorouracil for high-grade cervical dysplasia in human immunodeficiency virus infection: a randomized trial. *Obstet Gynecol*. Dec 1999;94(6):954-961. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10576182.

140. Shah K, Kashima H, Polk BF, Shah F, Abbey H, Abramson A. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstet Gynecol*. Dec 1986;68(6):795-799. Available at http://www.ncbi.nlm.nih.gov/pubmed/3785792.
141. Morrison EA, Gammon MD, Goldberg GL, Vermund SH, Burk RD. Pregnancy and cervical infection with human papillomaviruses. *Int J Gynaecol Obstet*. Aug 1996;54(2):125-130. Available at http://www.ncbi.nlm.nih.gov/pubmed/9236309.
142. Kjellberg L, Hallmans G, Ahren AM, Johansson R, Bergman F, Wadell G, Angström T, Dillner J. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *Br J Cancer*. 2000;82(7):1332-1338. Available at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed& Cmd=ShowDetailView&TermToSearch =10755410&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.
143. Audisio T, Roca FC, Piatti C. Topical imiquimod therapy for external anogenital warts in pregnant women. *Int J Gynaecol Obstet*. Mar 2008;100(3):275-276. Available at http://www.ncbi.nlm.nih.gov/pubmed/18035356.
144. Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol*. Jan 2006;21(1):1-2. Available at http://www.ncbi.nlm.nih.gov/pubmed/16039826.
145. Ciavattini A, Tsiroglou D, Vichi M, Di Giuseppe J, Cecchi S, Tranquilli AL. Topical Imiquimod 5% cream therapy for external anogenital warts in pregnant women: report of four cases and review of the literature. *J Matern Fetal Neonatal Med*. Jul 2012;25(7):873-876. Available at http://www.ncbi.nlm.nih.gov/pubmed/21815878.
146. Silverberg M, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obstet Gynecol*. 2003 Apr;101(4):645-52. 2003.
147. Fife KH, Katz BP, Brizendine EJ, Brown DR. Cervical human papillomavirus deoxyribonucleic acid persists throughout pregnancy and decreases in the postpartum period. *Am J Obstet Gynecol*. May 1999;180(5):1110-1114. Available at http://www.ncbi.nlm.nih.gov/pubmed/10329863.
148. Puranen MH, Yliskoski MH, Saarikoski SV, Syrjanen KJ, Syrjanen SM. Exposure of an infant to cervical human papillomavirus infection of the mother is common. *Am J Obstet Gynecol*. May 1997;176(5):1039-1045. Available at http://www.ncbi.nlm.nih.gov/pubmed/9166165.
149. Watts DH, Koutsky LA, Holmes KK, et al. Low risk of perinatal transmission of human papillomavirus: results from a prospective cohort study. *Am J Obstet Gynecol*. Feb 1998;178(2):365-373. Available at http://www.ncbi.nlm.nih.gov/pubmed/9500501.
150. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol*. Jan 1998;91(1):92-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/9464728.
151. Tenti P, Zappatore R, Migliora P, Spinillo A, Belloni C, Carnevali L. Perinatal transmission of human papillomavirus from gravidas with latent infections. *Obstet Gynecol*. Apr 1999;93(4):475-479. Available at http://www.ncbi.nlm.nih.gov/pubmed/10214817.
152. Orr JW, Jr., Barrett JM, Orr PF, Holloway RW, Holimon JL. The efficacy and safety of the cytobrush during pregnancy. *Gynecol Oncol*. Mar 1992;44(3):260-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/1541438.
153. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol*. Dec 2009;114(6):1179-1188. Available at http://www.ncbi.nlm.nih.gov/pubmed/19935017.

Hepatitis B Virus Infection (Last updated April 22, 2015; last reviewed June 14, 2017)

NOTE: Update in Progress

Epidemiology

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide.[1,2] Globally and in North America, approximately 10% of HIV-infected patients have evidence of chronic HBV infection.[3-5]

In countries with a low prevalence of endemic chronic HBV infection, the virus is transmitted primarily through sexual contact and injection drug use, whereas perinatal and early childhood exposures are responsible for most HBV transmission in higher prevalence regions.[1,2,6] Although the general modes of transmission are similar to HIV, HBV is transmitted more efficiently than HIV.[1,2] HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of jaundice and 60 days (range 40–90 days) from exposure to onset of abnormal liver enzymes. Genotypes of HBV (A–H) have been identified with different geographic distributions. Genotype A is most common among patients in North America and Western Europe.

Clinical Manifestations

Acute infection is usually asymptomatic. When they manifest, symptoms may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. Most patients with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue, until they develop cirrhosis and signs of portal hypertension (i.e., ascites, variceal bleeding, coagulopathy, jaundice, or hepatic encephalopathy). Hepatocellular carcinoma (HCC) is asymptomatic in its early stages and usually, but not always, occurs in the setting of HBV - or hepatitis C (HCV)-related cirrhosis.

Diagnosis

All HIV-infected patients should be tested for HBV infection because of shared routes of transmission. Initial testing should include serologic testing for surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs). In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure and anti-HBc immunoglobulin M is usually detectable at the onset of symptoms.

Chronic HBV infection is defined as persistent HBsAg detected on 2 occasions at least 6 months apart. Patients with chronic HBV infection should be further tested for HBV e-antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. Active disease, which can be HBeAg-negative or HBeAG-positive, can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevation. Patients whose past infection has resolved are HBsAg-negative with positive anti-HBs and anti-HBc, although cccDNA may remain in hepatocyte nuclei. Seroreversion may occur (becoming serum HBsAg-positive again) under severe immune suppression, as is seen with rituximab therapy or after stem cell transplant.[7,8]

The presence of anti-HBc alone, often occurs on testing as an isolated anti-HBc test result, usually signifies infection with HBV in the past with subsequent loss of anti-HBs. It occurs in 6.6% to 58.6% of HIV-infected patients,[9-11] Incidence of HBV viremia in HIV-infected patients with the isolated anti-HBc pattern ranges from 1% to 36%.[10,12-15] The clinical significance of isolated anti-HBc is unknown[16-18,20] but it may indicate chronic or, more likely, resolved infection in HIV-infected individuals.[16,17,21] In a low-prevalence country such as the United States, isolated anti-HBc may also represent a false-positive result.[16-19] HIV-infected patients have a higher frequency of isolated anti-HBc, particularly those with underlying HCV coinfection.[19,22,23]

Diagnosis of Disease Progression and the Role of Assessment of Liver Fibrosis

Compared with HIV-uninfected individuals, those who are HIV-infected have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[24] In HBV-monoinfected individuals, HBV DNA suppression, anti-HBe seroconversion (to anti-HBe-seronegativity), HBsAg loss, and acquisition of anti-HBs are all associated with a decreased incidence of cirrhosis, HCC,[25-27] and improved survival.[28-31] In comparison, the predictive value of these parameters in persons with HIV/HBV coinfection indicate they usually are more likely to have detectable HBeAg,[24,32] lower rates of seroconversion to anti-HBe, and increased risk of HCC, liver-related mortality and morbidity.[33,34]

HBV infection can result in a dynamic disease with a number of phases that are associated with either active or inactive chronic hepatitis. Duration of disease phases is different in those who acquire infection as neonates and young children compared with those who acquire infection as adults. Adults do not have an "immune-tolerant" phase (high levels of HBV DNA and low or rising ALT levels). Clinicians should be knowledgeable about these phases for HBV-monoinfected patients to determine who needs treatment and who should be monitored. In HIV/HBV coinfection, monitoring and treatment are also focused on the simultaneous treatment of both viruses.

HBV-monoinfected patients who are HBeAg-seropositive usually have high HBV DNA levels (>20,000 IU/mL) and abnormal ALT levels. However, with perinatal infection or infection acquired in early childhood, patients initially have an immune tolerance phase, with the presence of HBeAg, normal ALT levels, and high levels of HBV DNA but minimal or no liver disease. These patients may develop HBeAg-positive chronic hepatitis B with elevated ALT levels and remain at risk for HCC, cirrhosis, and flares of HBV.[35]

Anti-HBe seroconversion usually implies a transition from active disease to an inactive carrier state.[35] This transition can be spontaneous or associated with effective HBV treatment. In some instances, increased levels of ALT may precede a decline in HBV DNA that is accompanied by anti-HBe seroconversionp, that is, loss of HBeAg and development of anti-HBe. However, such spontaneous HBeAg conversion rates in HIV-infected patients appear to be lower than in monoinfected patients. The inactive chronic HBV state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level <2,000 IU/mL. Patients in the inactive state remain at risk of reactivation of HBV and development of HCC, but the risk is lower than for individuals with active HBV replication. In any patient, the re-emergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions. Although levels of HBV DNA are usually lower, HBeAg-negative patients experience an unrelenting but fluctuating course of disease progression, with fluctuating HBV DNA levels.[35] Thus, even in a patient without HBeAg, serum ALT and HBV DNA levels still should be monitored.

Patients diagnosed with chronic HBV infection should have a complete blood count, ALT, aspartate aminotransferase (AST), albumin and bilirubin levels, and prothrombin time monitored at baseline and every 6 months thereafter to assess severity and progression of liver disease. Patients with chronic HBV are at increased risk of HCC and imaging studies every 6 months are recommended in those who are cirrhotic, Asian male and older than age 40, Asian female and older than age 50, or male older than age 20 and from sub-Saharan Africa, as individuals in all of these groups are at increased risk of disease progression.[35]

Persistent low-level serum ALT abnormalities may be associated with significant liver disease, although normal ALT levels also may be seen in the setting of cirrhosis. Transient or persistent elevations in serum ALT levels can occur before loss of HBeAg, on discontinuation of anti-HBV therapy, and in association with emergence of HBV drug resistance.

Assessment of stage of liver fibrosis is important to know when to initiate esophageal variceal and HCC screening in cirrhotic patients. Fibrosis stage can be determined by liver biopsy or by noninvasive methods such as transient elastography, The decision to perform a liver biopsy should be individualized, especially given Department of Health and Human Services recommendations to initiate antiretroviral therapy (ART)-containing anti-HBV drugs regardless of CD4 T lymphocyte (CD4) cell count in HIV/HBV coinfected

patients.[36] There is increasing evidence that noninvasive methods (i.e., elastometry and serum biochemical indices) to evaluate liver fibrosis can be used to determine fibrosis in HBV.37-40 For example, one study demonstrated that transient elastography was able to discriminate moderate to severe fibrosis from mild fibrosis in HIV/HBV coinfection.[41]

Preventing Exposure

HBV is primarily transmitted by percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, HIV-infected patients should be counseled about transmission risks for HBV and avoidance of behaviors associated with such transmission **(AIII)**. Such counseling should emphasize sexual transmission as well as the risks associated with sharing needles and syringes, tattooing or body-piercing.

Preventing Disease

All household members and sexual contacts of patients with HBV should be screened and all susceptible contacts should receive both hepatitis A (HAV) and HBV vaccines regardless of whether they are HIV-infected **(AII)**. HBV immunization is the most effective way to prevent HBV infection and its consequences. All HIV-infected patients without chronic HBV or immunity to HBV should be vaccinated with HBV vaccine **(AII)** or with the combined HAV and HBV vaccine **(AII)**. This is of special importance in patients with high-risk behaviors associated with HBV infection and not on cART containing HBV-active drugs.[42] All non-immune patients should be tested annually for both anti-HBs (immunity to HBV) and HBsAg (for infection).

Prevaccination screening should include HBsAg, anti-HBs, and anti-HBc. A patient who is seropositive for anti-HBc and anti-HBs has resolved infection and does not need vaccination. Similarly, the presence of anti-HBs alone at levels >10 IU/mL is consistent with seroprotection, usually from vaccination,[43] and no further vaccinations are required. The interpretation is less clear in individuals with isolated anti-HBc. Aside from false-positive results, this pattern may signify infection in the distant past with subsequent loss of anti-HBs.[44] Most HIV-infected patients with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection. They should be vaccinated with a complete series of HBV vaccine followed by anti-HBs testing **(BII)**.[23,45]

The magnitude and duration of immunogenicity to HBV vaccination in HIV-infected adults is significantly lower than in HIV-seronegative healthy adults.[46-49] Factors associated with poor response to vaccine include low CD4 cell counts,[47,50-55] presence of detectable HIV RNA,[51,55,56] coinfection with HCV, occult HBV infection (a rare situation of unclear clinical significance), and the general health status of the host.[15,23,57-61] Based on these data, early vaccination is recommended in HIV-infected patients before CD4 cell counts decline to <350 cells/mm^3 **(AII)**. However, in patients who present to care at a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 because some HIV-infected patients with CD4 counts <200 cells/mm^3 do respond to vaccination **(AII)**. Given decreased vaccine responses among HIV-infected patients compared to HIV-uninfected individuals, anti-HBs titers should be obtained 1 month after completion of the vaccine series. For patients with anti-HBs levels <10 IU/mL, a second vaccine series is recommended **(BIII)**, although some specialists might delay revaccination until after a sustained increase in CD4 cell count is achieved on ART **(CIII)**. Two randomised controlled trials have shown that using four doses of double-dose vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine,[62,63] and one study also showed a higher overall response rate.[63] Some specialists consider this approach—four vaccinations—improves immunologic response in HIV-infected individuals either as an initial vaccination schedule or in patients who are non-responders **(BI)**. However, whether a schedule of four double-dose vaccines is superior to 4 single-dose or 3 double-dose vaccines is still unclear. Another study suggested that HIV-infected patients with CD4 counts >350 cells/mm^3 had improved responses when vaccinated with a double-dose vaccine on a 0-, 1-, and 6-month schedule.[50] Although other approaches have been investigated to improve responses, such as the use of combined hepatitis A and B vaccine,[64,65] or the use

of adjuvants;66 data are insufficient to support a broad recommendation for these approaches at this time. While additional studies are needed to determine optimal vaccination strategies in patients with advanced immunosuppression, the vaccination series for HBV should be initiated at first visit regardless of CD4 cell count.[67]

HAV vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users **(AIII)**. Responses to the HAV vaccine are reduced in HIV-infected patients with CD4 counts <200 cells/mm^3.[68,69] Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm^3 **(BIII)**.

Patients with chronic HBV disease should be advised to avoid alcohol consumption **(AIII)**.

Treating Disease

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV monoinfection: to prevent disease progression and to reduce HBV-related morbidity and mortality. To this end, treatment for HBV is intertwined with that for HIV.

Special Considerations with Regard to Starting ART

Regardless of CD4 cell count or need for HBV treatment, ART that includes agents with activity against both HIV and HBV is recommended for all patients coinfected with HIV and HBV. **(AII)**. For HIV/HBV coinfected individuals, ART MUST include two drugs active against HBV, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA **(AIII)**. Such a regimen will reduce the likelihood of immune reconstitution inflammatory syndrome (IRIS) against HBV and reduce risk of resistance that could occur with newer regimens such as with abacavir/lamivudine backbone.

If the patient refuses ART there are few options that can be used for treatment of HBV alone. Directly acting HBV drugs must not be given in the absence of a fully suppressive ART regimen. This is because most drugs active against HBV also are active against HIV (anti-HBV drugs such as tenofovir, entecavir, emtricitabine, lamivudine, adefovir, and possibly telbivudine), but when given without more potent anti-HIV agents, can produce drug-resistant HIV in the recipient **(AII)**. Alternative HBV therapy for patients who refuse initiation of ART would be 48 weeks of pegylated interferon (IFN) (see below).

The Department of Health and Human Services guidelines for treatment of HIV infection recommend the fixed-dose coformulation of tenofovir/emtricitabine or abacavir/lamivudine as recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones for ART-naive patients.[36] Because both tenofovir and emtricitabine have anti-HBV activity, it is also the treatment of choice for HIV/HBV coinfected patients **(AIII)**. Tenofovir is active against wild-type and lamivudine-resistant HBV strains. Studies in HBV/HIV-coinfected patients (most of them carrying lamivudine-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[70-75] Tenofovir has a high genetic barrier for development of resistance mutations. However, the nephrotoxicity associated with tenofovir may limit its use in some patients. In patients who have renal dysfunction or are at high risk of developing renal dysfunction, entecavir can be added to a fully suppressive ART regimen **(BIII)**. Chronic administration of lamivudine or emtricitabine as the only active drug against HBV **should be avoided** because of the high rate of selection of HBV drug-resistance mutations **(AI)**.

Most patients receiving ART should continue HBV therapy indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell counts, and because discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30% of cases,[76,77] with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.[47,78-80] If anti-HBV therapy and ART must be discontinued, transaminase levels should be monitored every 6 weeks for 3 months and every 3 to 6 months thereafter. If a flare occurs, anti-HBV therapy and ART should be

reinstituted and can be potentially lifesaving **(AIII)**.

Alternative Treatment of HBV in HIV-Infected Patients Who Are Not Receiving ART

In general, HBV and HIV co-treatment is recommended. But if ART cannot be given or the patient refuses HIV treatment or is a long-term non-progressor, treatment for active HBV disease is indicated.[35] Specifically, anti-HBV therapy is indicated for individuals with elevated ALT and elevated HBV DNA >2,000 IU/mL or significant fibrosis **(AI)**.[35] All patients with advanced liver disease or cirrhosis should also be treated. Additional information on HBV treatment indications is found in the American Association for the Study of Liver Diseases (AASLD) guidelines.[35]

For HIV/HBV-coinfected patients not receiving ART who meet criteria for HBV therapy as described above, pegylated interferon-alfa-2a alone might be considered and is the only option that will not predispose to antiretroviral (ARV) drug resistance in HIV when used in the absence of ART **(CIII)**. Adefovir alone is of limited value in this setting because it is less potent and has a higher risk of selecting for resistance mutations than the preferred HBV nucleos(t)ides.[35] However, data are limited on the use of these agents alone in the HIV/HBV-coinfected population. Patients who are HBeAg-positive, infected with HBV genotype A, in the early stages of liver disease, and have high ALT levels are the most likely to benefit from pegylated IFN- alfa **(CIII)**, which requires a defined course of 48 weeks. Tenofovir, entecavir, lamivudine, emtricitabine, and telbivudine **should not be used** in the absence of ART because of the development of HIV-resistance mutations.[81,82] If there is no indication for HBV treatment, continued monitoring and reassessment of risk of liver-related morbidity and mortality is required because HBV is a dynamic disease that can change with time.

Some HIV/HBV-coinfected patients also have chronic HCV infection. There is scant information on the treatment of HBV/HCV/HIV coinfection. Because patients with HBV, HCV, and HIV appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[83-85] attempts should be made to treat both hepatitis viruses, if feasible. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed (see Hepatitis C Infection) **(CIII)**. If ART is not desired, IFN-alfa-based therapy, which has activity against both HCV and HBV, should be considered **(CIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

In order to prevent emergence of drug-resistant variants and evaluate response for patients on nucleos(t)ide analogues, treatment response should be monitored by testing for HBV DNA at 12-week intervals. HBeAg also should be tested every 6 to12 months in patients who are HBeAg-positive. Treatment responses are defined as follows:

- Primary non-response is an HBV DNA <1 $\log_{10}$ decline at 12 weeks.[86]
- A complete virologic response is an undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.[86]
- A partial virologic response is ≥1 $\log_{10}$ decline but still detectable HBV DNA at Week 24.[86]
- A maintained virologic response is a response that continues while on therapy, and a sustained virologic response is one that is still present 6 months after stopping therapy.

For patients who are HBeAg-positive, loss of HBeAg is also a measure of virologic response. Other markers that indicate treatment success include improvement in liver histology based on biopsy or noninvasive markers, normalization of serum aminotransferases, and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response; however, this desirable serologic response is uncommon.[35]

Major toxicities of IFN-alfa (pegylated or standard) are flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and psychiatric reactions including depression, insomnia, irritability, anxiety. Other common reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Nucleos(t)ide analogs: Renal toxicity with tenofovir, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent in HIV-infected patients with underlying renal insufficiency, older patients or those treated for prolonged periods.[87] These biochemical changes are usually reversible on discontinuation of tenofovir.

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, and urinalysis every 6 months. Because renal toxicity may be reversible, alternative anti-HBV therapy should be used if renal toxicity occurs **(AI)**. If tenofovir is used in patients with baseline renal insufficiency, dose adjustment as noted in the package insert is required.

Entecavir-associated lactic acidosis is uncommon but has been reported in HBV-monoinfected patients with advanced cirrhosis.[88] Telbivudine can cause creatine phosphokinase (CPK) elevations >7 times the upper limit of normal, with some reports of myopathy.[89] Thus, CPK should be measured at baseline, every 3 to 6 months, and if musculoskeletal symptoms develop. If CPK levels are elevated, telbivudine should be discontinued and replaced with another anti-HBV agent **(AI)**.

Adefovir causes renal tubular disease at doses of 30 mg/day or higher, but this toxicity is uncommon at the recommended 10 mg/day dose. In HBV-monoinfected patients, incidence of increased creatinine levels with 5 years of adefovir therapy ranges from 3% to 8%.[90,91]

Immune Reconstitution Inflammatory Syndrome (IRIS)

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called "hepatitis flare",[92] which constitutes IRIS in HIV/HBV-coinfected persons. IRIS may be manifested by dramatic increases in serum aminotransferase levels as CD4 cell counts rise within the first 6 to 12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis. After introduction of ART, serum ALT levels should be monitored closely; some experts recommend ALT testing at 6 and 12 weeks, then every 3 to 6 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated International Normalized Ratio and low serum albumin) should prompt consultation with a hepatologist.

Flares are worse in patients with more severe liver disease, especially in those with cirrhosis.[93] Distinguishing between ARV-associated hepatotoxicity or other causes of hepatitis (acute hepatitis A, C, D or E virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus) and IRIS may be difficult. ARV-associated hepatotoxicity may be dose-dependent or idiosyncratic. The risk of hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases (ALT, aspartate aminotransferase) and the presence of HBV or HCV coinfection before initiation of ART.[94-101] However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80%–90%) coinfected patients do not have hepatotoxicity,[97] and clinically significant hepatotoxicity (elevated direct bilirubin) is rare; aminotransferase levels return to baseline in most cases, even if the offending medication is continued.[95,102] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless patients have symptoms of hypersensitivity (e.g., fever, lymphadenopathy, rash), symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice), or elevations in serum aminotransferase levels >10 times the upper limit of normal. However, the development of jaundice is associated with severe morbidity and mortality and the offending drug(s) should be discontinued **(AIII)**.[103]

The major problem in managing ALT flares is distinguishing between drug-induced liver injury and HBV reactivation, IRIS, emergence of drug resistance, and HBeAg seroconversion. In drug-induced liver toxicity, determining the offending medication also can be challenging. A review of the medication history and testing for serum HBV DNA, HBeAg, HIV RNA levels, and CD4 cell count can help distinguish between these possibilities. Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If the flare is severe or HBV drug resistance is suspected, then consultation with a hepatologist is recommended. Other causes of abnormal liver tests should be sought,

including use of drugs or alcohol, other viral hepatitis infections (hepatitis A, C, D, and E), and nonalcoholic fatty liver disease.

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogues is defined as primary nonresponse after 12 weeks of therapy in patients who consistently adhere to HBV therapy or an increase in HBV DNA levels greater than 1 $\log_{10}$ above nadir. In either situation, treatment failure is generally due either to drug-resistant HBV if on lamivudine/emtricitabine monotherapy or noncompliance. If drug-resistant HBV is present, a change in treatment needs to be made **(AII)**. Distinct resistance patterns exist with the different groups of anti-HBV drugs: the L-nucleosides (telbivudine, lamivudine, emtricitabine); acyclic phosphonates/nucleotides (adefovir and tenofovir); and D-cyclopentane (entecavir), which shares some resistance mutations with the L-nucleosides. Many experts will obtain HBV-resistance testing because it has value in distinguishing between noncompliance and resistance, evaluating patients with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir. However, tenofovir has not been associated with clinical resistance, although slow response has been noted as discussed above. Addition of entecavir has led to suppression of HBV DNA in these slow-to-respond patients.[104]

Lamivudine (or emtricitabine) monotherapy for HBV leads to emergence of drug-resistant HBV increasingly with time on treatment and **should not be used** as the sole anti-HBV drug in an ART regimen **(AII)**. The rate of development of lamivudine resistance is approximately 20% per year in HIV/HBV-coinfected patients treated with lamivudine alone.[105] If lamivudine resistance is suspected or documented, tenofovir should be added **(BIII)**.[106-108] Because patients with lamivudine-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, emtricitabine), and partial resistance to entecavir, those agents **should not be used** in patients found to have lamivudine-resistant HBV **(AI)**.[109] All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and Table 8.

If treatment failure occurs on entecavir, then the only rational choice is replacement with tenofovir (+/- emtricitabine) because of the cross resistance that occurs with L-nucleosides (telbivudine, lamivudine, emtricitabine) **(AI)**.

Patients whose HBV initially fails to respond to pegylated IFN-alfa can be given nucleos(t)ide analogue therapy following the recommendations previously described **(CIII)**.

If treatment failure with tenofovir occurs, particularly in lamivudine- or emtricitabine-experienced patients, then entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII)**. However, documented *in vivo* resistance to tenofovir has not yet been reported. Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly in patients who are receiving an HBV drug, with high potency and a high genetic barrier to resistance, such as tenofovir, but they may still be detectable for some years. Thus, in a compliant patient with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels **(BII)**. Improvement of response with the addition of entecavir has been reported, but whether such "intensification therapy" is required is unclear. Nonetheless, patients on drugs that are less potent or that have a lower barrier to resistance, such as adefovir or L-nucleosides, who have partial virologic responses (<2 $\log_{10}$ drop in HBV DNA levels from baseline at 24 weeks) should be switched to a more potent regimen such as tenofovir with emtricitabine or entecavir (if treatment-naive) because of the risk of development of drug resistance to the intial therapy **(BII)**.

Special considerations for treating end-stage liver disease

Treatment of end-stage liver disease in HIV/HBV-coinfected patients should be managed as it is in HIV-seronegative patients. These patients should be referred to a hepatologist. As with monoinfected patients, IFN-alfa is **contraindicated** in end-stage liver disease **(AI)**, but nucleoside analogs are safe and efficacious **(AI)**.[105,110,111] All patients with ascites should undergo paracentesis to exclude spontaneous bacterial

peritonitis (SBP).[112] Management of ascites includes sodium restriction (<2 g/day) and the recommended diuretic regimen is spironolactone combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone) **(AI)**. All patients who have had SBP and those with ascites total protein <1 g/dL should receive prophylaxis against SBP with administration of oral antibiotics such as norfloxacin (400 mg/day), ciprofloxacin 750 mg/week or trimethoprim-sulfamethoxazole (one double-strength tablet/day) **(AI)**.[113]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all patients with cirrhosis at the time of diagnosis and then every 1 to 2 years to identify substantial gastroesophageal varices (see American Association for the Study of Liver Diseases guidelines). Patients with varices require non-selective beta blockers, such as nadolol or propranolol, that are the mainstay of both primary and secondary prevention of variceal hemorrhage. Esophageal variceal banding is another preventive option, particularly for those who cannot tolerate beta blockers. Hepatic encephalopathy is treated with a 40-g protein diet and the use of non-absorbable disaccharides such as lactulose and/or non-absorbable antibiotics such as rifaximin.

Patients with HBV-related cirrhosis are at increased risk of HCC[114] and should be screened every 6 to 12 months with imaging studies, as recommended in HBV monoinfection. Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center and whether the patient has cirrhosis. Usually ultrasound is the initial preferred imaging modality. HCC can occur without cirrhosis and HIV coinfection appears to increase the risk of HCC in HBV,[115] but more frequent screening in HIV/HBV coinfection has not been studied, and so is not recommended. HIV/HBV-coinfected patients with decompensated liver disease and/or early HCC are candidates for orthotopic liver transplantation. HIV infection is not a contraindication to organ transplantation with the use of effective ART.[116] Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required **(AII)**.

Preventing Recurrence

As previously indicated, most patients should continue HBV therapy (with the exception of pegylated IFN) indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell counts, and because reports of hepatitis flares after discontinuation of lamivudine in those who have not reached treatment endpoints can be extrapolated to other HBV-active drugs.[78-80]

Special Considerations During Pregnancy

Pregnant women, including HIV-infected women, should be screened for HBsAg, anti-HBc, and anti-HBs. Those who are HBsAg- and anti-HBs-negative should be offered vaccination against HBV. Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk of pre-term labor and delivery may be increased with acute HBV infection.

High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.[117-120] Although a high viral load is clearly important, it is not the only factor predisposing to prophylaxis failure, as demonstrated by a case report in which perinatal HBV transmission occurred despite suppression of HBV DNA to undetectable levels in the mother with antepartum lamivudine and appropriate immunoprophylaxis of the infant.[121,122]

ART including drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection, including pregnant women, who require HBV treatment or who are initiating ART for their own health. Because combination ART is recommended for all HIV-infected women during pregnancy to prevent perinatal transmission of HIV, even if it is not required for their own health, all HIV/HBV-coinfected pregnant women should receive an ART regimen containing HBV-active drugs. This is because of concern about potential IRIS-related flare of HBV activity after initiation of ART, even in women with relatively high CD4 cell counts, if drugs without anti-HBV activity are used. In addition, using drugs with anti-HBV

activity during pregnancy will lower HBV levels and decrease the risk that HBIG and HBV vaccine will fail to prevent perinatal transmission of HBV. Following delivery, considerations regarding the continuation of ARV drugs in mothers are the same as in other adults who are not pregnant. Therefore, once HBV therapy with nucleos(t)ide analogs is initiated, treatment is recommended to be continued indefinitely. However, if ARV drugs are discontinued postpartum, frequent monitoring of liver function tests for potential HBV flare is recommended, with prompt reinitiation of treatment for both HIV and HBV, should a flare occur.

Tenofovir given in combination with lamivudine or emtricitabine, is the preferred dual-NRTI backbone for pregnant women with chronic HBV infection **(AIII)**, as it is in nonpregnant HIV/HBV-coinfected individuals.[124] Because emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV, the recommended dual-NRTI backbone for HIV/HBV-coinfected individuals who are not pregnant is tenofovir/emtricitabine or tenofovir/lamivudine **(AI)**. Of the ARV agents with activity against hepatitis B, the one used most often in pregnancy is lamivudine. As of July 2013, more than 4,000 cases of pregnancy outcomes after first-trimester exposure to lamivudine have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure.[123] Lamivudine has been well tolerated by pregnant women and is a recommended NRTI for use in pregnancy **(AII)**.[124] Similarly, no increase in birth defects has been noted in 1400 cases of first-trimester exposure to emtricitabine, which is an alternative NRTI for use in pregnancy (http://www.apregistry.com) **(BII)**.[123] Tenofovir was not teratogenic in animals, but at high doses, reversible bone changes were seen in multiple animal species. A total of 1,982 cases of first-trimester exposure to tenofovir have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects noted.[123]

Several other ARV agents with activity against HBV, including adefovir and telbivudine, have been evaluated and found not to be teratogenic in animals, but experience in the first trimester with these agents in human pregnancy is limited. These drugs could be included in a regimen during pregnancy if other options are inappropriate. Each of these agents should be administered only in combination with a fully suppressive ARV regimen because of the risk of development of ARV drug resistance. Entecavir was associated with skeletal anomalies in rats and rabbits, but only at high, maternally-toxic doses. Data on use of entecavir and adefovir in human pregnancy are not available. Telbivudine was given to 95 HBV-seropositive, HIV-seronegative women during the third trimester in one study, and it was well tolerated with no birth defects observed. Cases of exposure during pregnancy to any of the ARV and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com).

IFN-alfa formulations are not recommended for use in pregnancy. Although these agents are not teratogenic, they are abortifacient at high doses in monkeys and **should not be used** in pregnant women because of their direct antigrowth and antiproliferative effects **(AII)**.[125]

Infants born to HBsAg-positive women should receive HBIG and HBV vaccine within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and hepatitis B vaccine within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 1 of 2)

Preventing HBV Infection

Indications for HBV Vaccination:

- Patients without chronic HBV infection or without immunity to HBV (anti-HBs <10 IU/mL) **(AII)**
- Patients with isolated anti-HBc and with negative HBV DNA **(BII)**.
- Early vaccination is recommended before CD4 count falls below 350 cells/mm^3 **(AII)**, as low CD4 count at time of vaccination has been associated with poor response to the vaccine.
- However, in a patient with low baseline CD4 cell count, vaccination should not be deferred until CD4 reaches >350 cells/mm^3, as some patients with CD4 <200 cells/mm3 do respond to vaccination **(AII)**.

Vaccination Schedule:

- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months **(AII)**; or
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2 and 6 months **(BI)**; or
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months) (**AII)**
- Anti-HBs should be obtained 1 month after completion of the vaccine series, anti-HBs <10 IU/mL will be considered as non-responders. **(BIII)**

For Vaccine Non-Responders:

- Revaccinate with a second vaccine series **(BIII)**
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART **(CIII)**.

Alternative Vaccine Dose for Non-Responders:

- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2 and 6 months **(BI)**,

Treating HBV Infection

Indication for Therapy:

- All HIV/HBV coinfected patients, regardless of CD4 count (AII). Treatment should be used for both HIV and HBV infections **(AIII)**.

Preferred Therapy:

- The ART regimen must include 2 drugs active against HBV, preferably with tenofovir 300 mg + emtricitabine 200 mg (or lamivudine 300 mg) PO once daily **(AIII)**.

Duration of Therapy:

- Most patients on treatment for HBV and HIV will receive therapy indefinitely **(CIII)**.

Alternative Therapy

If ART cannot be given or if the patient refuses ART, or is a HIV long-term non-progressor:

- Anti-HBV therapy is indicated for elevated ALT, and HBV DNA >2,000 IU/mL, significant liver fibrosis, advanced liver disease or cirrhosis **(AI)**.
- Peg-IFN-alfa 2a 180 mcg SQ once weekly for 48 weeks **(CIII)**, *or*
- Peg-IFN- alfa 2b 1.5 mcg/kg SQ once weekly for 48 weeks **(CIII)**

If tenofovir cannot be used as part of the ART regimen because of current or high risk of renal dysfunction:

- A fully suppressive ART regimen without tenofovir should be used, with the addition of entecavir to the regimen **(BIII)**

Note: Chronic administration of emtricitabine or lamivudine monotherapy for HBV infection **should be avoided** in most cases due to high rate of selection of HBV drug resistance mutation **(AI)**.

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 2 of 2)

Other Considerations:

- HAV vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users **(AIII)**
- Antibody responses to HAV should be assessed 1 month after completion of vaccination series. If HAV Ab IgG is negative, patients should be revaccinated when the CD4 count is >200 cells/mm^3 **(BIII)**.
- Directly acting HBV drugs (such as tenofovir, entecavir, emtricitabine, lamivudine, adefovir, and possibly telbivudine) must not be given in the absence of a fully suppressive ART regimen to avoid selection of drug resistant HIV **(AI)**.
- As patients with HBV/HCV/HIV coinfection appear to have accelerated liver fibrosis progression, high risk of HCC, and increased mortality, treatment for both HBV and HCV infection should be initiated, if feasible.
- When changing ART regimens, it is crucial to continue agents with anti-HBV activity **(BIII)**.
- If anti-HBV therapy must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3-6 months thereafter.
- If a hepatic flare occurs after drug discontinuation, HBV therapy should be re-instituted, as it can be potentially life saving **(AIII)**.

Key to Acronyms: ab = antibody; anti-HBs = hepatitis B surface antibody; ALT = alanine transferease; ART = antiretroviral therapy; CD4 = CD4 T-lymphocyte cell; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; IgG = immunoglobulin; IM = intramuscular; PO = orally; SQ = subcutaneous

References

1. Lee WM. Hepatitis B virus infection. *N Engl J Med*. 1997;337(24):1733-1745. Available at http://www.ncbi.nlm.nih.gov/pubmed/9392700.
2. Levine OS, Vlahov D, Koehler J, Cohn S, Spronk AM, Nelson KE. Seroepidemiology of hepatitis B virus in a population of injecting drug users. Association with drug injection patterns. *Am J Epidemiol*. 1995;142(3):331-341. Available at http://www.ncbi.nlm.nih.gov/pubmed/7631637.
3. Alter MJ. Epidemiology of viral hepatitis and HIV coinfection. *J Hepitol*. 2006;44(1 Suppl):S6-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/16352363.
4. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology*. 2009;49(5 Suppl):S138-145. Available at http://www.ncbi.nlm.nih.gov/pubmed/19399813.
5. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. *N Engl J Med*. 2012;366(19):1749-1752. Available at http://www.ncbi.nlm.nih.gov/pubmed/22571198.
6. Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol*. 1977;105(2):94-98. Available at http://www.ncbi.nlm.nih.gov/pubmed/835566.
7. Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. *JAMA*. 2013;310(16):1664. Available at http://www.ncbi.nlm.nih.gov/pubmed/24150447.
8. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer*. 2013;49(16):3486-3496. Available at http://www.ncbi.nlm.nih.gov/pubmed/23910494.
9. Palacios R, Mata R, Hidalgo A, et al. Very low prevalence and no clinical significance of occult hepatitis B in a cohort of HIV-infected patients with isolated anti-HBc seropositivity: the BHOI study. *HIV Clin Trials*. 2008;9(5):337-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/18977722.
10. Neau D, Winnock M, Jouvencel AC, et al. Occult hepatitis B virus infection in HIV-infected patients with isolated antibodies to hepatitis B core antigen: Aquitaine cohort, 2002-2003. *Clin Infect Dis*. 2005;40(5):750-753. Available at http://www.ncbi.nlm.nih.gov/pubmed/15714424.
11. Lo Re V, 3rd, Wertheimer B, Localio AR, et al. Incidence of transaminitis among HIV-infected patients with occult hepatitis B. *J Clin Virol*. 2008;43(1):32-36. Available at http://www.ncbi.nlm.nih.gov/pubmed/18486540.
12. Tsui JI, French AL, Seaberg EC, et al. Prevalence and long-term effects of occult hepatitis B virus infection in HIV-infected women. *Clin Infect Dis*. 2007;45(6):736-740. Available at http://www.ncbi.nlm.nih.gov/pubmed/17712758.

13. Tien PC, Kovacs A, Bacchetti P, et al. Association between syphilis, antibodies to herpes simplex virus type 2, and recreational drug use and hepatitis B virus infection in the Women's Interagency HIV Study. *Clin Infect Dis.* 2004;39(9):1363-1370. Available at http://www.ncbi.nlm.nih.gov/pubmed/15494914.

14. Filippini P, Coppola N, Pisapia R, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. *AIDS*. 2006;20(9):1253-1260. Available at http://www.ncbi.nlm.nih.gov/pubmed/16816553.

15. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004;36(3):869-875. Available at http://www.ncbi.nlm.nih.gov/pubmed/15213572.

16. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol*. 2000;62(4):450-455. Available at http://www.ncbi.nlm.nih.gov/pubmed/11074473.

17. Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis*. 1998;17(1):6-13. Available at http://www.ncbi.nlm.nih.gov/pubmed/9512175.

18. Silva AE, McMahon BJ, Parkinson AJ, Sjogren MH, Hoofnagle JH, Di Bisceglie AM. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. *Clin Infect Dis.* 1998;26(4):895-897. Available at http://www.ncbi.nlm.nih.gov/pubmed/9564471.

19. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. *Clin Infect Dis.* 2013;56(4):606-612. Available at http://www.ncbi.nlm.nih.gov/pubmed/23090927.

20. Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. *Hepatology*. 1988;8(4):766-770. Available at http://www.ncbi.nlm.nih.gov/pubmed/2968945.

21. Ponde RA, Cardoso DD, Ferro MO. The underlying mechanisms for the 'anti-HBc alone' serological profile. *Arch Virol*. 2010;155(2):149-158. Available at http://www.ncbi.nlm.nih.gov/pubmed/20091193.

22. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. *J Infect Dis*. 2005;191(9):1435-1441. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809901.

23. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. *J Acquir Immune Defic Syndr*. 2003;34(4):439-441. Available at http://www.ncbi.nlm.nih.gov/pubmed/14615664.

24. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology*. 1999;29(4):1306-1310. Available at http://www.ncbi.nlm.nih.gov/pubmed/10094979.

25. Harris RA, Chen G, Lin WY, Shen FM, London WT, Evans AA. Spontaneous clearance of high-titer serum HBV DNA and risk of hepatocellular carcinoma in a Chinese population. *Cancer Causes Control*. 2003;14(10):995-1000. Available at http://www.ncbi.nlm.nih.gov/pubmed/14750539.

26. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*. 2006;130(3):678-686. Available at http://www.ncbi.nlm.nih.gov/pubmed/16530509.

27. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295(1):65-73. Available at http://www.ncbi.nlm.nih.gov/pubmed/16391218.

28. Fattovich G, Olivari N, Pasino M, D'Onofrio M, Martone E, Donato F. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut*. 2008;57(1):84-90. Available at http://www.ncbi.nlm.nih.gov/pubmed/17715267.

29. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology*. 2002;35(6):1522-1527. Available at http://www.ncbi.nlm.nih.gov/pubmed/12029639.

30. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med*. 1996;334(22):1422-1427. Available at http://www.ncbi.nlm.nih.gov/pubmed/8618580.

31. Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology*. 1997;113(5):1660-1667. Available at http://www.ncbi.nlm.nih.gov/pubmed/9352870.

32. Gilson RJ, Hawkins AE, Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS*. 1997;11(5):597-606. Available at http://www.ncbi.nlm.nih.gov/pubmed/9108941.

33. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926. Available at http://www.ncbi.nlm.nih.gov/pubmed/12493258.

34. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepitol*. 2007;47(4):527-537. Available at http://www.ncbi.nlm.nih.gov/pubmed/17692986.

35. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-662. Available at http://www.ncbi.nlm.nih.gov/pubmed/19714720.

36. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed April 13, 2015.

37. Myers RP, Tainturier MH, Ratziu V, et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. *J Hepitol*. 2003;39(2):222-230. Available at http://www.ncbi.nlm.nih.gov/pubmed/12873819.

38. Poynard T, Vergniol J, Ngo Y, et al. Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest(R)) and elastography (FibroScan(R)). *J Hepitol*. 2014;61(5):994-1003. Available at http://www.ncbi.nlm.nih.gov/pubmed/25016224.

39. Lee HW, Yoo EJ, Kim BK, et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. *Am J Gastroenterol*. 2014;109(8):1241-1249. Available at http://www.ncbi.nlm.nih.gov/pubmed/24957159.

40. Leroy V, Sturm N, Faure P, et al. Prospective evaluation of FibroTest(R), FibroMeter(R), and HepaScore(R) for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. *J Hepitol*. 2014;61(1):28-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24631902.

41. Miailhes P, Pradat P, Chevallier M, et al. Proficiency of transient elastography compared to liver biopsy for the assessment of fibrosis in HIV/HBV-coinfected patients. *J Viral Hepat*. 2011;18(1):61-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/20196798.

42. Heuft MM, Houba SM, van den Berk GE, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. Available at http://www.ncbi.nlm.nih.gov/pubmed/24685742.

43. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med*. 1986;315(4):209-214. Available at http://www.ncbi.nlm.nih.gov/pubmed/2941687.

44. Witt MD, Seaberg EC, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984-2011. *Clin Infect Dis*. 2013;57(1):77-84. Available at http://www.ncbi.nlm.nih.gov/pubmed/23532480.

45. Jongjirawisan Y, Ungulkraiwit P, Sungkanuparph S. Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response. *J Med Assoc Thai*. 2006;89(12):2028-2034. Available at http://www.ncbi.nlm.nih.gov/pubmed/17214053.

46. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep*. 2006;55(RR-16):1-33; quiz CE31-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/17159833.

47. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine*. 2000;18(13):1161-1165. Available at http://www.ncbi.nlm.nih.gov/pubmed/10649616.

48. Loke RH, Murray-Lyon IM, Coleman JC, Evans BA, Zuckerman AJ. Diminished response to recombinant hepatitis B vaccine in homosexual men with HIV antibody: an indicator of poor prognosis. *J Med Virol*. 1990;31(2):109-111. Available at http://www.ncbi.nlm.nih.gov/pubmed/2143776.

49. Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. *AIDS*. 1994;8(4):558-559. Available at http://www.ncbi.nlm.nih.gov/pubmed/7912087.

50. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine*. 2005;23(22):2902-2908. Available at http://www.ncbi.nlm.nih.gov/pubmed/15780739.

51. Veiga AP, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naive) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine*. 2006;24(49-50):7124-7128. Available at http://www.ncbi.nlm.nih.gov/pubmed/16884833.

52. Bruguera M, Cremades M, Salinas R, Costa J, Grau M, Sans J. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. *J Clin Gastroenterol*. 1992;14(1):27-30. Available at http://www.ncbi.nlm.nih.gov/pubmed/1532609.

53. Keet IP, van Doornum G, Safary A, Coutinho RA. Insufficient response to hepatitis B vaccination in HIV-positive homosexual men. *AIDS*. 1992;6(5):509-510. Available at http://www.ncbi.nlm.nih.gov/pubmed/1535502.

54. Ristola MA, Vuola JM, Valle M, von Reyn CF. Antibody responses to intradermal recombinant hepatitis B immunization among HIV-positive subjects. *Vaccine*. 2004;23(2):205-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/15531038.

55. Tedaldi EM, Baker RK, Moorman AC, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. *Clin Infect Dis*. 2004;38(10):1478-1484. Available at http://www.ncbi.nlm.nih.gov/pubmed/15156488.

56. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis*. 2005;41(7):1045-1048. Available at http://www.ncbi.nlm.nih.gov/pubmed/16142673.

57. Lee SD, Chan CY, Yu MI, Lu RH, Chang FY, Lo KJ. Hepatitis B vaccination in patients with chronic hepatitis C. *J Med Virol*. 1999;59(4):463-468. Available at http://www.ncbi.nlm.nih.gov/pubmed/10534727.

58. Wiedmann M, Liebert UG, Oesen U, et al. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. *Hepatology*. 2000;31(1):230-234. Available at http://www.ncbi.nlm.nih.gov/pubmed/10613751.

59. Anthony DD, Yonkers NL, Post AB, et al. Selective impairments in dendritic cell-associated function distinguish hepatitis C virus and HIV infection. *J Immunol*. 2004;172(8):4907-4916. Available at http://www.ncbi.nlm.nih.gov/pubmed/15067070.

60. Sarobe P, Lasarte JJ, Casares N, et al. Abnormal priming of CD4(+) T cells by dendritic cells expressing hepatitis C virus core and E1 proteins. *J Virol*. 2002;76(10):5062-5070. Available at http://www.ncbi.nlm.nih.gov/pubmed/11967322.

61. Auffermann-Gretzinger S, Keeffe EB, Levy S. Impaired dendritic cell maturation in patients with chronic, but not resolved, hepatitis C virus infection. *Blood*. 2001;97(10):3171-3176. Available at http://www.ncbi.nlm.nih.gov/pubmed/11342445.

62. Chaiklang K, Wipasa J, Chaiwarith R, Praparattanapan J, Supparatpinyo K. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. *PloS one*. 2013;8(11):e80409. Available at http://www.ncbi.nlm.nih.gov/pubmed/24265819.

63. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA*. 2011;305(14):1432-1440. Available at http://www.ncbi.nlm.nih.gov/pubmed/21486976.

64. Wolters B, Muller T, Ross RS, et al. Comparative evaluation of the immunogenicity of combined hepatitis A and B vaccine by a prospective and retrospective trial. *Hum Vaccin*. 2009;5(4):248-253. Available at http://www.ncbi.nlm.nih.gov/pubmed/19276678.

65. Tung J, Carlisle E, Smieja M, Kim PT, Lee CH. A randomized clinical trial of immunization with combined hepatitis A and B versus hepatitis B alone for hepatitis B seroprotection in hemodialysis patients. *Am J Kidney Dis*. 2010;56(4):713-719. Available at http://www.ncbi.nlm.nih.gov/pubmed/20630640.

66. Cooper CL, Davis HL, Angel JB, et al. CPG 7909 adjuvant improves hepatitis B virus vaccine seroprotection in antiretroviral-treated HIV-infected adults. *AIDS*. 2005;19(14):1473-1479. Available at http://www.ncbi.nlm.nih.gov/pubmed/16135900.

67. Whitaker JA, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. *Lancet*. 2012;12(12):966-976. Available at http://www.ncbi.nlm.nih.gov/pubmed/23174382.

68. Weinberg A, Huang S, Fenton T, et al. Virologic and immunologic correlates with the magnitude of antibody responses to the hepatitis A vaccine in HIV-infected children on highly active antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2009;52(1):17-24. Available at http://www.ncbi.nlm.nih.gov/pubmed/19617848.

69. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med*. 2005;118 Suppl 10A:75S-83S. Available at http://www.ncbi.nlm.nih.gov/pubmed/16271546.

70. van Bommel F, Wunsche T, Schurmann D, Berg T. Tenofovir treatment in patients with lamivudine-resistant hepatitis B mutants strongly affects viral replication. *Hepatology*. 2002;36(2):507-508. Available at http://www.ncbi.nlm.nih.gov/pubmed/12143063.

71. Nunez M, Perez-Olmeda M, Diaz B, Rios P, Gonzalez-Lahoz J, Soriano V. Activity of tenofovir on hepatitis B virus replication in HIV-coinfected patients failing or partially responding to lamivudine. *AIDS*. 2002;16(17):2352-2354. Available at http://www.ncbi.nlm.nih.gov/pubmed/12441815.

72. Ristig MB, Crippin J, Aberg JA, et al. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. *J Infect Dis*. 2002;186(12):1844-1847. Available at http://www.ncbi.nlm.nih.gov/pubmed/12447773.

73. Nelson M, Portsmouth S, Stebbing J, et al. An open-label study of tenofovir in HIV-1 and Hepatitis B virus coinfected individuals. *AIDS*. 2003;17(1):F7-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/12478090.

74. Benhamou Y, Tubiana R, Thibault V. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. *N Engl J Med*. 2003;348(2):177-178. Available at http://www.ncbi.nlm.nih.gov/pubmed/12519935.

75. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44(5):1110-1116. Available at http://www.ncbi.nlm.nih.gov/pubmed/17058225.

76. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS*. 2010;24(6):857-865. Available at http://www.ncbi.nlm.nih.gov/pubmed/20216301.

77. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus coinfected patients: the Swiss HIV Cohort Study. *HIV Med*. 2009;10(1):12-18. Available at http://www.ncbi.nlm.nih.gov/pubmed/18795964.

78. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*. 1999;28(5):1032-1035. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452630.

79. Proia LA, Ngui SL, Kaur S, Kessler HA, Trenholme GM. Reactivation of hepatitis B in patients with human immunodeficiency virus infection treated with combination antiretroviral therapy. *Am J Med*. 2000;108(3):249-251. Available at http://www.ncbi.nlm.nih.gov/pubmed/10723980.

80. Neau D, Schvoerer E, Robert D, et al. Hepatitis B exacerbation with a precore mutant virus following withdrawal of lamivudine in a human immunodeficiency virus-infected patient. *J Infect*. 2000;41(2):192-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/11023772.

81. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356(25):2614-2621. Available at http://www.ncbi.nlm.nih.gov/pubmed/17582071.

82. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356(14):1445-1454. Available at http://www.ncbi.nlm.nih.gov/pubmed/17409326.

83. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr*. 2000;24(3):211-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/10969344.

84. Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. *AIDS*. 2004;18(15):2039-2045. Available at http://www.ncbi.nlm.nih.gov/pubmed/15577625.

85. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer*. 1998;75(3):347-354. Available at http://www.ncbi.nlm.nih.gov/pubmed/9455792.

86. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepitol*. 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22436845.

87. Nishijima T, Kawasaki Y, Tanaka N, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS*. 2014;28(13):1903-1910. Available at http://www.ncbi.nlm.nih.gov/pubmed/25259702.

88. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology*. 2009;50(6):2001-2006. Available at http://www.ncbi.nlm.nih.gov/pubmed/19937695.

89. Liaw YF, Gane E, Leung N, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology*. 2009;136(2):486-495. Available at http://www.ncbi.nlm.nih.gov/pubmed/19027013.

90. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology*. 2006;131(6):1743-1751. Available at http://www.ncbi.nlm.nih.gov/pubmed/17087951.

91. Marcellin P, Chang TT, Lim SG, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2008;48(3):750-758. Available at http://www.ncbi.nlm.nih.gov/pubmed/18752330.

92. Lau GK. Does treatment with interferon-based therapy improve the natural history of chronic hepatitis B infection? *J Hepitol*. 2007;46(1):6-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/17112628.

93. Crane M, Oliver B, Matthews G, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. *J Infect Dis*. 2009;199(7):974-981. Available at http://www.ncbi.nlm.nih.gov/pubmed/19231993.

94. Kontorinis N, Dieterich D. Hepatotoxicity of antiretroviral therapy. *AIDS Rev*. 2003;5(1):36-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/12875106.

95. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. 2003;34 Suppl 1:S21-33. Available at http://www.ncbi.nlm.nih.gov/pubmed/14562855.

96. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/10632283.

97. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS*. 2004;18(17):2277-2284. Available at http://www.ncbi.nlm.nih.gov/pubmed/15577540.

98. Torti C, Lapadula G, Casari S, et al. Incidence and risk factors for liver enzyme elevation during highly active antiretroviral therapy in HIV-HCV coinfected patients: results from the Italian EPOKA-MASTER Cohort. *BMC Infect Dis*. 2005;5:58. Available at http://www.ncbi.nlm.nih.gov/pubmed/16018804.

99. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS*. 2001;15(10):1261-1268. Available at http://www.ncbi.nlm.nih.gov/pubmed/11426070.

100. Meraviglia P, Schiavini M, Castagna A, et al. Lopinavir/ritonavir treatment in HIV antiretroviral-experienced patients: evaluation of risk factors for liver enzyme elevation. *HIV Med*. 2004;5(5):334-343. Available at http://www.ncbi.nlm.nih.gov/pubmed/15369508.

101. Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996-1998. Groupe dEpidemiologie Clinique de Sida en Aquitaine (GECSA). *AIDS*. 1999;13(17):F115-121. Available at http://www.ncbi.nlm.nih.gov/pubmed/10597772.

102. Sherman KE, Shire NJ, Cernohous P, et al. Liver injury and changes in hepatitis C Virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naive HCV-HIV-coinfected patients: lopinavir-ritonavir versus nelfinavir. *Clin Infect Dis.* 2005;41(8):1186-1195. Available at http://www.ncbi.nlm.nih.gov/pubmed/16163639.

103. Reuben A. Hy's law. *Hepatology*. 2004;39(2):574-578. Available at http://www.ncbi.nlm.nih.gov/pubmed/14768020.

104. Luetkemeyer AF, Charlebois ED, Hare CB, et al. Resistance patterns and response to entecavir intensification among HIV-HBV-coinfected adults with persistent HBV viremia. *J Acquir Immune Defic Syndr*. 2011;58(3):e96-99. Available at http://www.ncbi.nlm.nih.gov/pubmed/22005002.

105. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology*. 1999;30(5):1302-1306. Available at http://www.ncbi.nlm.nih.gov/pubmed/10534354.

106. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. 2009;23(13):1707-1715. Available at http://www.ncbi.nlm.nih.gov/pubmed/19584701.

107. Vassiliadis TG, Giouleme O, Koumerkeridis G, et al. Adefovir plus lamivudine are more effective than adefovir alone in lamivudine-resistant HBeAg- chronic hepatitis B patients: a 4-year study. *J Gastroenterol Hepatol*. 2010;25(1):54-60. Available at http://www.ncbi.nlm.nih.gov/pubmed/19780875.

108. Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology*. 2007;133(5):1445-1451. Available at http://www.ncbi.nlm.nih.gov/pubmed/17983801.

109. Ze E, Baek EK, Lee JJ, et al. Long-term outcomes of two rescue therapies in lamivudine-refractory patients with chronic hepatitis B: combined lamivudine and adefovir, and 1-mg entecavir. *Clin and Molec Hepatol*. 2014;20(3):267-273. Available at http://www.ncbi.nlm.nih.gov/pubmed/25320730.

110. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med*. 1998;339(2):61-68. Available at http://www.ncbi.nlm.nih.gov/pubmed/9654535.

111. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med*. 1999;341(17):1256-1263. Available at http://www.ncbi.nlm.nih.gov/pubmed/10528035.

112. Runyon BA, Practice Guidelines Committee AAftSoLD. Management of adult patients with ascites due to cirrhosis. *Hepatology*. 2004;39(3):841-856. Available at http://www.ncbi.nlm.nih.gov/pubmed/14999706.

113. Singh N, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Int Med*. 1995;122(8):595-598. Available at http://www.ncbi.nlm.nih.gov/pubmed/7887554.

114. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology*. 1997;26(3 Suppl 1):34S-38S. Available at http://www.ncbi.nlm.nih.gov/pubmed/9305661.

115. Salmon-Ceron D, Rosenthal E, Lewden C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalite 2005 study. *J Hepitol*. 2009;50(4):736-745. Available at http://www.ncbi.nlm.nih.gov/pubmed/19231018.

116. Miro JM, Laguno M, Moreno A, Rimola A, Hospital Clinic Olt In Hiv Working G. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? *J Hepitol*. 2006;44(1 Suppl):S140-145. Available at http://www.ncbi.nlm.nih.gov/pubmed/16352366.

117. del Canho R, Grosheide PM, Schalm SW, de Vries RR, Heijtink RA. Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepitol*. 1994;20(4):483-486. Available at http://www.ncbi.nlm.nih.gov/pubmed/8051386.

118. Ngui SL, Andrews NJ, Underhill GS, Heptonstall J, Teo CG. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factors. *Clin Infect Dis.* 1998;27(1):100-106. Available at http://www.ncbi.nlm.nih.gov/pubmed/9675462.

119. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust*. 2009;190(9):489-492. Available at http://www.ncbi.nlm.nih.gov/pubmed/19413519.

120. Kubo A, Shlager L, Marks AR, et al. Prevention of vertical transmission of hepatitis B: an observational study. *Ann Int Med*. 2014;160(12):828-835. Available at http://www.ncbi.nlm.nih.gov/pubmed/24862434.

121. Kazim SN, Wakil SM, Khan LA, Hasnain SE, Sarin SK. Vertical transmission of hepatitis B virus despite maternal lamivudine therapy. *Lancet*. 2002;359(9316):1488-1489. Available at http://www.ncbi.nlm.nih.gov/pubmed/11988251.

122. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/25227594.

123. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 January 2012. 2012. Wilmington, NC.

124. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed April 13, 2015

125. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology*. 2005;65(6):807-811. Available at http://www.ncbi.nlm.nih.gov/pubmed/16186517.

Hepatitis C Virus Infection (Last updated October 28, 2014; last reviewed October 28, 2014)

Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus; the estimated worldwide prevalence of HCV infection is 2% to 3%, which translates to an estimated 170 million infected individuals of whom approximately 3.2 million live in the United States.[1] Seven distinct HCV genotypes have been described.[2] Genotype 1 infection accounts for approximately 75% of infections in the United States and approximately 90% of infections among blacks.[3,4] Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, through sexual intercourse, and from a mother to her infant; however, the relative efficiency of transmission by these routes varies substantially. Approximately, 20% to 30% of HIV-infected patients in the United States are coinfected with HCV.[5,6]

HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.[7-9] Transmission via injection drug use remains the most common mode of acquisition in the United States while transmission through contaminated blood products is now rare. Health care-associated transmission of HCV also can occur as a result of improper reuse of parenteral medications and equipment.[10-12] Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Heterosexual transmission of HCV is uncommon but more likely in those whose partners are coinfected with HIV and HCV.[13,14] Existing data also suggest that sexual contact is a relatively inefficient mode of transmission between HIV seronegative men who have sex with men (MSM).[15] However, in HIV-infected MSM, multiple outbreaks of acute HCV infection demonstrate that sexual transmission is an important mode of acquisition in this population.[16] Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted diseases (STDs).[15,17-19,20,21] Temporally, the increase in the incidence of sexual transmission of HCV among HIV-infected MSMs coincides with an increase in high-risk sexual behaviors following the introduction of antiretroviral therapy (ART).[22,23]

Mother-to-child transmission of HCV infection occurs in approximately 1% to 3% of infants born to HCV-seropositive mothers without and 4% to 7% of infants born to HCV-seropositive mothers with detectable plasma HCV RNA levels.[24-27] Incidence of mother-to-child HCV transmission is increased when mothers are HIV-coinfected, reaching rates of 10% to 20%.[28,29]

Clinical Manifestations

Both acute and chronic HCV infections are usually minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have characteristic symptoms, including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels may be the only laboratory finding during acute and chronic infection. Recognition of acute HCV infection in patients with new-onset liver enzyme elevations is clinically important since HCV treatment during the early phases of infection is more efficacious than treatment during the chronic phase.[30,31]

Cirrhosis develops in approximately 20% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.[32,33] Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.[33,34] HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly in those with advanced immunodeficiency (CD4 T-

lymphocyte [CD4] count <200 cells/mm^3).[35,36] Further, coinfected patients with cirrhosis progress more rapidly to life-limiting outcomes such as end-stage liver disease and hepatocellular carcinoma (HCC) than do those who are HCV-monoinfected.[37,38] Because of its high prevalence and accelerated progression, HCV disease is a leading non-AIDS cause of death in HIV-infected individuals.[39-41] In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all HIV-infected patients should undergo routine HCV screening. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.[42] For at risk HCV-seronegative individuals, HCV antibody testing is recommended annually or as indicated by risk exposure.

False-negative anti-HCV antibody results are possible but are uncommon (<1%) in HIV-infected patients with advanced immunosuppression.[43,44] In addition, negative anti-HCV antibody results can occur during acute infection. Following acute HCV infection, the duration of the window period prior to seroconversion is highly variable, ranging from 2 weeks to 12 weeks. Serum ALT levels are frequently elevated early in the course of acute infection and high ALT levels should prompt testing for HCV RNA if serologic test results are negative or indeterminate in individuals at risk of HCV infection.[45]

Individuals who test positive for HCV antibody should undergo confirmatory testing by using a sensitive quantitative assay to measure plasma HCV RNA level. Importantly, plasma HCV RNA viral load does not correlate with HCV disease severity, and therefore, should not be monitored serially in patients not taking HCV treatment. Plasma HCV RNA levels do provide important prognostic information about the likelihood of response to HCV treatment.

Preventing Exposure

The primary route of HCV transmission is drug injection via a syringe or other injection paraphernalia (i.e., "cookers," filters, or water) previously used by an infected person. HCV-seronegative injection drug users should be encouraged to stop using injection drugs by entering a substance abuse treatment program or, if they are unwilling or unable to stop, to reduce the risk of transmission by never sharing needles or injection equipment.[46-48] HCV also can be transmitted sexually, especially between HIV-infected MSM. HCV-seronegative patients must be counseled regarding the risk of sexual acquisition. The effectiveness of male condoms in reducing HCV transmission is unknown, nonetheless, barrier precautions are strongly recommended to reduce the risk of STDs, including HCV **(BIII)**.[49]

Preventing Disease

There is no vaccine or recommended post-exposure prophylaxis to prevent HCV infection. Following acute HCV infection, chronic infection may be prevented within the first 6 to 12 months after infection through antiviral treatment; relatively high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.[50,51] However, patients also have the potential for spontaneous clearance after acute infection; as such, some experts recommend observation of acutely infected patients—particularly those whose infection (e.g., those with C/C IL28B genotype) is more likely to resolve—for approximately 3 to 6 months before initiating HCV treatment.[52] In the setting of evolving data, recommendations for management of acute HCV infection in HIV-infected patients are expected to change rapidly. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most up-to-date guidance.

HCV-infected individuals should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (as alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day), and avoiding iron

supplementation in the absence of documented iron deficiency.[53] HCV-infected patients should be tested for previous or concurrent hepatitis B virus (HBV) infection because co-infection with HBV is associated with increased morbidity. Those without evidence of immunity to HBV should be vaccinated (see Hepatitis B Virus Infection section). Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in HCV-infected individuals, these patients should be screened for immunity (HAV IgG or antibody total) and those susceptible should be vaccinated **(BIII)**.

Coinfected patients with cirrhosis are at risk of life-threatening complications and should be managed in consultation with a gastroenterologist or hepatologist. In particular, individuals with cirrhosis should undergo serial screening for HCC;[54] some experts recommend performing ultrasonography at 6- to 12-month intervals, although the optimal screening strategy is unknown. Because of its relatively poor specificity and sensitivity, alfa-fetoprotein should not be the sole screening method. HIV infection is not an absolute contraindication to liver transplantation; accordingly, coinfected patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression. Coinfected patients should be treated with ART in accordance with the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* developed by the Department of Health and Human Services Panel.[55] Dose adjustment of certain ARV agents may be needed in patients with decompensated cirrhosis.

Treating Disease

In general, the goals of therapy, treatment regimen, and monitoring parameters for HIV/HCV coinfected patients are similar to those recommended for HCV monoinfected patients. The field of HCV drug development is evolving rapidly. The armamenarium of approved drugs is likely to expand considerably in the next few years. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most up-to-date recommendations.

Special Considerations During Pregnancy

Pregnant HIV-infected women should be tested for HCV infection to allow appropriate management for the mothers during pregnancy and after delivery, and also for their infants.[56] HCV treatment with PegIFN and ribavirin is **contraindicated** during pregnancy **(AII)**. IFNs are abortifacient at high doses in monkeys and **should not be used** in pregnant women because of their direct antigrowth and antiproliferative effects.[57] Ribavirin is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia. Ribavirin **should not be used** during pregnancy **(AII)**. Women of childbearing potential and men receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy **(AIII)**. Inadvertent pregnancy during paternal exposure was not associated with adverse events in two newborns.[58] Pregnancies that occur in women taking ribavirin or those in women whose male partner is taking the drug should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com). Telaprevir, boceprevir, and sofosbuvir are Pregnancy Category B and simeprevir is Pregnancy Category C; however, these agents are often used in combination with PegIFN/ribavirin, which are **not recommended** in pregnancy. The FDA category assignment for these novel drugs, though, is based on safety in animal studies as there are no human data available.

Evaluation of HCV-infected pregnant women, including liver biopsy, can be delayed until >3 months after delivery to allow potential pregnancy-related changes in disease activity to resolve. HAV and HBV vaccines can be administered during pregnancy and women who have not previously been vaccinated should receive them. Several studies have reported that perinatal transmission of HCV occurs more frequently in women with HIV/HCV-coinfection than in those with HCV monoinfection. However, data are limited regarding the role of

medical or surgical interventions to reduce the risk of perinatal HCV transmission. Nearly all studies, including those in HIV-uninfected and HIV-infected women, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.[26,59-61] Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.[62-65] Thus, while elective cesarean delivery in HIV/HCV-coinfected women can be considered based on HIV-related indications, data are insufficient to support its routine use for prevention of HCV transmission.

References

1. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol*. 2007;13(17):2436-2441. Available at http://www.ncbi.nlm.nih.gov/pubmed/17552026.
2. Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. *JAMA*. 2007;297(7):724-732. Available at http://www.ncbi.nlm.nih.gov/pubmed/17312292.
3. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144(10):705-714. Available at http://www.ncbi.nlm.nih.gov/pubmed/16702586.
4. Blatt LM, Mutchnick MG, Tong MJ, et al. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *J Viral Hepat*. 2000;7(3):196-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/10849261.
5. Staples CT, Jr., Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 1999;29(1):150-154. Available at http://www.ncbi.nlm.nih.gov/pubmed/10433578.
6. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2002;34(6):831-837. Available at http://www.ncbi.nlm.nih.gov/pubmed/11833007.
7. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA*. 2002;288(2):199-206. Available at http://www.ncbi.nlm.nih.gov/pubmed/12095384.
8. Ciesek S, Friesland M, Steinmann J, et al. How stable is the hepatitis C virus (HCV)? Environmental stability of HCV and its susceptibility to chemical biocides. *J Infect Dis*. 2010;201(12):1859-1866. Available at http://www.ncbi.nlm.nih.gov/pubmed/20441517.
9. Paintsil E, He H, Peters C, Lindenbach BD, Heimer R. Survival of hepatitis C virus in syringes: implication for transmission among injection drug users. *J Infect Dis*. 2010;202(7):984-990. Available at http://www.ncbi.nlm.nih.gov/pubmed/20726768.
10. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *J Hepatol*. 2006;45(4):607-616. Available at http://www.ncbi.nlm.nih.gov/pubmed/16901579.
11. Alter MJ. Healthcare should not be a vehicle for transmission of hepatitis C virus. *J Hepatol*. 2008;48(1):2-4. Available at http://www.ncbi.nlm.nih.gov/pubmed/18023493.
12. Centers for Disease C, Prevention. Acute hepatitis C virus infections attributed to unsafe injection practices at an endoscopy clinic--Nevada, 2007. *MMWR*. Morbidity and mortality weekly report. 2008;57(19):513-517. Available at http://www.ncbi.nlm.nih.gov/pubmed/18480743.
13. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). *Ann Intern Med*. 1991;115(10):764-768. Available at http://www.ncbi.nlm.nih.gov/pubmed/1656825.
14. Lissen E, Alter HJ, Abad MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus infected index cases. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):827-831. Available at http://www.ncbi.nlm.nih.gov/pubmed/7509282.
15. van de Laar TJ, van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *J Infect Dis*. 2007;196(2):230-238. Available at

http://www.ncbi.nlm.nih.gov/pubmed/17570110.

16. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *AIDS*. 2010;24(12):1799-1812. Available at http://www.ncbi.nlm.nih.gov/pubmed/20601854.
17. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2005;41(3):395-402. Available at http://www.ncbi.nlm.nih.gov/pubmed/16007539.
18. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS*. 2007;21(8):983-991. Available at http://www.ncbi.nlm.nih.gov/pubmed/17457092.
19. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. *Gastroenterology*. 2009;136(5):1609-1617. Available at http://www.ncbi.nlm.nih.gov/pubmed/19422083.
20. Fierer DS, Uriel AJ, Carriero DC, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. *J Infect Dis*. 2008;198(5):683-686. Available at http://www.ncbi.nlm.nih.gov/pubmed/18627270.
21. Taylor LE, Holubar M, Wu K, et al. Incident hepatitis C virus infection among US HIV-infected men enrolled in clinical trials. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2011;52(6):812-818. Available at http://www.ncbi.nlm.nih.gov/pubmed/21282184.
22. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA*. 2004;292(2):224-236. Available at http://www.ncbi.nlm.nih.gov/pubmed/15249572.
23. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS*. 2004;18(2):303-309. Available at http://www.ncbi.nlm.nih.gov/pubmed/15075549.
24. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *The New England Journal of Medicine*. 1994;330(11):744-750. Available at http://www.ncbi.nlm.nih.gov/pubmed/8107740.
25. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology*. 2002;36(5 Suppl 1):S106-113. Available at http://www.ncbi.nlm.nih.gov/pubmed/12407583.
26. McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315 e311-315. Available at http://www.ncbi.nlm.nih.gov/pubmed/18771997.
27. Valladares G, Chacaltana A, Sjogren MH. The management of HCV-infected pregnant women. *Ann Hepatol*. 2010;9 Suppl:92-97. Available at http://www.ncbi.nlm.nih.gov/pubmed/20714003.
28. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-1889. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267758.
29. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006;44(1 Suppl):S6-9. Available at http://www.ncbi.nlm.nih.gov/pubmed/16352363.
30. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *The New England Journal of Medicine*. 2001;345(20):1452-1457. Available at http://www.ncbi.nlm.nih.gov/pubmed/11794193.
31. Kamal SM, Fouly AE, Kamel RR, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology*. 2006;130(3):632-638. Available at http://www.ncbi.nlm.nih.gov/pubmed/16530503.
32. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *The New England Journal of Medicine*. 1995;332(22):1463-1466. Available at http://www.ncbi.nlm.nih.gov/pubmed/7739682.
33. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832. Available at

http://www.ncbi.nlm.nih.gov/pubmed/9121257.

34. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Elevated liver enzymes following initiation of antiretroviral therapy. *JAMA*. 2000;283(19):2526-2527. Available at http://www.ncbi.nlm.nih.gov/pubmed/10815113.
35. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology*. 1999;30(4):1054-1058. Available at http://www.ncbi.nlm.nih.gov/pubmed/10498659.
36. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology*. 2001;34(6):1193-1199. Available at http://www.ncbi.nlm.nih.gov/pubmed/11732009.
37. Pineda JA, Romero-Gomez M, Diaz-Garcia F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41(4):779-789. Available at http://www.ncbi.nlm.nih.gov/pubmed/15800956.
38. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11(11):1425-1430. Available at http://www.ncbi.nlm.nih.gov/pubmed/16237709.
39. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol*. 2005;42(6):799-805. Available at http://www.ncbi.nlm.nih.gov/pubmed/15973779.
40. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641. Available at http://www.ncbi.nlm.nih.gov/pubmed/16908797.
41. Smith JA, Aberle JH, Fleming VM, et al. Dynamic coinfection with multiple viral subtypes in acute hepatitis C. *J Infect Dis*. 2010;202(12):1770-1779. Available at http://www.ncbi.nlm.nih.gov/pubmed/21067369.
42. National Institutes of H. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. *Hepatology*. 2002;36(5 Suppl 1):S3-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/12407572.
43. Chamot E, Hirschel B, Wintsch J, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. *AIDS*. 1990;4(12):1275-1277. Available at http://www.ncbi.nlm.nih.gov/pubmed/1965126.
44. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. *J Clin Microbiol*. 2000;38(2):575-577. Available at http://www.ncbi.nlm.nih.gov/pubmed/10655348.
45. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. *Clin Liver Dis*. 2003;7(1):179-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/12691466.
46. Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health*. 1995;85(11):1531-1537. Available at http://www.ncbi.nlm.nih.gov/pubmed/7485666.
47. Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. Syringe exchange and risk of infection with hepatitis B and C viruses. *Am J Epidemiol*. 1999;149(3):203-213. Available at http://www.ncbi.nlm.nih.gov/pubmed/9927214.
48. Vlahov D, Junge B, Brookmeyer R, et al. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16(5):400-406. Available at http://www.ncbi.nlm.nih.gov/pubmed/9420320.
49. Centers for Disease C, Prevention. Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. MMWR. *Morbidity and mortality weekly report*. 2011;60(28):945-950. Available at http://www.ncbi.nlm.nih.gov/pubmed/21775948.
50. Lambers FA, Brinkman K, Schinkel J, et al. Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration. *AIDS*. 2011;25(10):1333-1336. Available at http://www.ncbi.nlm.nih.gov/pubmed/21516025.
51. Piroth L, Larsen C, Binquet C, et al. Treatment of acute hepatitis C in human immunodeficiency virus-infected patients:

the HEPAIG study. *Hepatology*. 2010;52(6):1915-1921. Available at http://www.ncbi.nlm.nih.gov/pubmed/21064156.

52. Grebely J, Petoumenos K, Hellard M, et al. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology*. 2010;52(4):1216-1224. Available at http://www.ncbi.nlm.nih.gov/pubmed/20803561.
53. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28(3):805-809. Available at http://www.ncbi.nlm.nih.gov/pubmed/9731576.
54. Forns X, Bruix J. Treating hepatitis C in patients with cirrhosis: the effort is worth it. *J Hepatol*. 2010;52(5):624-626. Available at http://www.ncbi.nlm.nih.gov/pubmed/20334945.
55. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed June 1, 2012
56. ACOG educational bulletin. Viral hepatitis in pregnancy. Number 248, July 1998 (replaces No. 174, November 1992). American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1998;63(2):195-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/9856330.
57. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology*. 2005;65(6):807-811. Available at http://www.ncbi.nlm.nih.gov/pubmed/16186517.
58. Hegenbarth K, Maurer U, Kroisel PM, Fickert P, Trauner M, Stauber RE. No evidence for mutagenic effects of ribavirin: report of two normal pregnancies. *The American Journal of Gastroenterology*. 2001;96(7):2286-2287. Available at http://www.ncbi.nlm.nih.gov/pubmed/11467687.
59. Ghamar Chehreh ME, Tabatabaei SV, Khazanehdari S, Alavian SM. Effect of cesarean section on the risk of perinatal transmission of hepatitis C virus from HCV-RNA+/HIV- mothers: a meta-analysis. *Arch Gynecol Obstet*. 2011;283(2):255-260. Available at http://www.ncbi.nlm.nih.gov/pubmed/20652289.
60. Marine-Barjoan E, Berrebi A, Giordanengo V, et al. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? *AIDS*. 2007;21(13):1811-1815. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690581.
61. European Paediatric Hepatitis CVN. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-1879. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267757.
62. Read JS, Tuomala R, Kpamegan E, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the women and infants transmission study. *J Acquir Immune Defic Syndr*. 2001;26(3):236-245. Available at http://www.ncbi.nlm.nih.gov/pubmed/11242196.
63. Grubert TA, Reindell D, Kastner R, et al. Rates of postoperative complications among human immunodeficiency virus-infected women who have undergone obstetric and gynecologic surgical procedures. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2002;34(6):822-830. Available at http://www.ncbi.nlm.nih.gov/pubmed/11850864.
64. Grubert TA, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky BH, Dathe O. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet*. 1999;354(9190):1612-1613. Available at http://www.ncbi.nlm.nih.gov/pubmed/10560681.
65. Fiore S, Newell ML, Thorne C, European HIViOG. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS*. 2004;18(6):933-938. Available at http://www.ncbi.nlm.nih.gov/pubmed/15060441.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] The virus has worldwide distribution, with a seroprevalence of 39% to 69% among adults.[3-6] Primary JCV infection usually occurs in childhood, without identified symptoms, and establishes a chronic asymptomatic carrier state in most individuals, which explains the detection of viral DNA in urine in 20% to 30% of adults who are immunologically normal.[4,7-11]

Outside the context of HIV infection, PML is rare and characteristically manifests as a complication of other immunocompromising diseases or therapies.[12-14] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab,[15] efalizumab,[16] infliximab,[17] and rituximab.[18] Concern has been raised about a possible increased risk of PML in HIV-infected patients treated with rituximab for non-Hodgkin lymphoma,[19,20] but no reports have yet documented PML in that setting.

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[21-23] and was almost invariably fatal; spontaneous remissions were rare.[24] With the widespread use of ART in the developed world, incidence of PML has decreased substantially,[25] whereas mortality in HIV-infected persons who develop the disease has remained high.[26-28] Unlike some of the other CNS opportunistic infections that are almost wholly prevented when CD4 T-lymphocyte (CD4 cell) counts are maintained above 100 to 200 cells/mm^3, PML can still appear in such patients and in those on ART.[2,29,30] Moreover, PML can develop in the setting of initiating ART and immune reconstitution, discussed below.[2,31]

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Any region of the CNS can be involved, although some areas seem to be more favored, including the occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[12] Spinal cord involvement is rare.[32] Although lesions can be multiple, one often is clinically predominant. Initial symptoms and signs often begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis) as individual lesions expand concentrically or along white matter tracts. The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs, rather than as a more diffuse encephalopathy, or isolated dementia or behavioral syndrome, all of which are uncommon without concomitant focal findings.[33]

The time course of this evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly. Headache and fever are not characteristic of the disease, except in severe cases of inflammatory PML (see below), but seizures develop in nearly 20% of PML patients and are associated with lesions immediately adjacent to the cortex.[34]

Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings. The first step is usually identifying the clinical picture of steady progression of focal neurological deficits. Magnetic resonance imaging (MRI) almost always confirms distinct white matter lesions in areas of the brain corresponding to the

clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The latter characteristic, though possibly subtle, helps to distinguish the PML lesion from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse, with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques, such as diffusion-weighted imaging and magenetic resonance (MR) spectroscopy, may provide additional diagnostic information.[35-37] New PML lesions and the advancing edge of large lesions have high signal on diffusion-weighted imaging and normal-to-low apparent diffusion coefficient signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. Older lesions and the centers of larger lesions have increased apparent diffusion coefficient values. MR spectroscopy typically shows decreased N-acetylaspartate and increased choline, related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[38]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Confirming the diagnosis, however, is invaluable. Certainly for atypical cases but even for typical cases, confirmation allows physicians to initiate ART rapidly and with certainty and prevents the need to revisit diagnosis when disease progression continues. Confirmed diagnosis also informs discussions of prognosis.

The usual first step in confirming the diagnosis is to test cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context, that is, those with subacute onset of focal neurological abnormalities and suggestive imaging findings.[9,39] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[40] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[41,42] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded (e.g., by PCR analyses of CSF for varicella zoster virus and Epstein-Barr virus for varicella zoster virus encephalitis and primary CNS lymphoma, respectively).

In some instances, brain biopsy is required to establish the diagnosis. PML can usually be identified by the characteristic tissue cytopathology, including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages, with identification of JCV or cross reacting polyoma virus by immunohistochemistry, *in situ* nucleic acid hybridization, or electron microscopy.[12,43,44]

Serologic testing generally is not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment[6] and it eventually may be applied to risk in HIV. Detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[45] but requires further prospective study.

Preventing Exposure

JCV has a worldwide distribution and, as previously noted, 20% to 60% of people exhibit serologic evidence of exposure by their late teens.[46] Currently, there is no known way to prevent exposure to the virus.

Preventing Disease

In many individuals, JCV likely continues as a latent and intermittently productive, although clinically silent, infection in the kidney or other systemic sites, and systemic infection may increase in the presence of immunosuppression. Whether JCV is also latent in the CNS or PML results from temporally more proximate hematogenous dissemination is the subject of debate.[47,48] Protection is conferred by either preventing spread to

the CNS or by preventing active viral replication with effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII)**.

Treating Disease

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. Treatment strategies depend on the patient's antiretroviral (ARV) treatment status and its effect. Thus, in patients with PML who are not on therapy, ART should be started immediately **(AII)**. In this setting, approximately half of HIV-infected PML patients experience a remission in which disease progression stops. Neurological deficits often persist, but some patients experience clinical improvement.[27,49-55] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[55] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another recent retrospective case series reported that 42% of PML survivors on ART had moderate-to-severe disability.[56] Peripheral blood CD4 cell count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 cell counts. In other case series, worse prognosis was also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and the presence of lesions in the brain stem.[30,49,51,52,54,55,57] Contrast enhancement on imaging may predict better outcome.[29]

ART should be optimized for virologic suppression in patients with PML who have received ART but remain HIV viremic because of inadequate adherence or ARV resistance **(AIII)**. More problematic are patients who develop PML despite successful virologic suppression while taking ART. A preliminary report of PML patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher than anticipated survival,[58] but it has not yet been followed by a full report or structured trial. Therefore, there is no evidence supporting ART intensification for PML.

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV effects.[59] One report found that at the beginning of the combination ART era, a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[60] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.

The history of more specifically targeted treatments for PML includes many anecdotal reports of success that have not been confirmed by controlled studies. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[61] Therefore, treatment with cytarabine is **not recommended (AII)**. Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.[40,53-55,62] Thus, treatment with cidofovir is also **not recommended (AII)**. A lipid-ester derivative, hexadecyloxypropyl-cidofovir, recently has been reported to suppress JCV replication in cell culture,[63] but its efficacy in HIV-associated PML is unknown.

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[64,65] drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[66]

although the rationale for this practice has been questioned.[67] Again, anecdotes about favorable outcomes[1,68-71] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, this class of drugs **cannot be recommended (BIII)**.

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[72] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[73] At this time, topotecan also is **not recommended (BIII)**.

A Phase I/II clinical trial of the antimalarial drug mefloquine recently was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsoring pharmaceutical company, however, because of lack of demonstrable efficacy (http://clinicaltrials.gov/ct2/show/NCT00746941). To date, the results have only been presented at a meeting and in abstract.[74]

Immunomodulatory approaches to the treatment of PML in HIV-infected patients also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[75] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha **cannot be recommended**.[76] A single report described failure of interferon-beta treatment of HIV-associated PML[77] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[15] Case reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome treated with interleukin-2.[78-80] Like the other reports, these, too, have not been followed up with more substantial trials.

Special Considerations with Regard to Starting ART

ART should be started in patients not on HIV treatment as soon as PML is recognized **(AII)**. For patients already on treatment who have demonstrated plasma viremia and are adherent to therapy, ART should be adjusted based on plasma virus susceptibility **(AII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Treatment response should be monitored with clinical examination and MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantitation of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress. In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response, and can serve as a further baseline for subsequent scans should the patient begin to deteriorate. In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII)**.

PML-Immune Reconstitution Inflammatory Syndrome

PML has been reported to occur within the first weeks to months after initiating ART[2,30,31,81,82] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course. This presentation has been referred to as inflammatory PML or PML-immune reconstitution inflammatory syndrome (PML-IRIS). Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[83-86] Further study is needed to determine whether the likelihood of detecting JCV in CSF is different in patients who have PML-IRIS than in those with classical PML.[49,87] Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses, but other undefined factors also may contribute to unmasked PML-IRIS. A similar,

though often more fulminant, form of PML-IRIS has been reported after discontinuation of natalizumab and plasma exchange in patients with multiple sclerosis who develop PML.[15,88,89]

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting, with reported benefit.[2,82] Further study of corticosteroids for PML is needed to confirm efficacy and refine dosage and duration. At present, however, use of the drugs appears justified for PML-IRIS characterized by contrast enhancement, edema or mass effect, and clinical deterioration **(BIII)**. The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response can be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids likely have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5 day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued at the standard therapeutic doses during this period **(AIII)**.

A single case report suggested that maraviroc might be beneficial for PML-IRIS,[90] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, it has not yet been followed by further studies.

Although some clinicians may want to use adjuvant corticosteroid therapy to treat all cases of PML regardless of whether there is evidence of IRIS, this action is not justified and should be discouraged in patients who have no evidence of substantial inflammation on contrast-enhanced neuroimaging or on pathological examination **(CIII)**. In patients whose condition worsens, imaging can be repeated to monitor for development of IRIS before initiating corticosteroids.

Managing Treatment Failure

Because PML remission can take several weeks, no strict criteria define treatment failure. However, a working definition may be continued clinical worsening and continued detection of CSF JCV without substantial decrease within 3 months. In the case of ART, plasma HIV RNA levels and blood CD4 cell count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for use of ART. When PML continues to worsen despite suppressive anti-HIV treatment, one of the unproven therapies described above can be considered, although the possibility of toxicity must be balanced against the unproven benefits of these treatments. Better treatments and rigorous assessment of them are needed.

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence.[53] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 cell counts **(AII)**.

Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant women as in women who are not pregnant. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

Recommendations for Preventing and Treating PML and JCV

- There is no effective antiviral therapy for preventing or treating JCV infections or PML.
- The main approach to treatment is to preserve immune function or reverse HIV-associated immunosuppression with effective ART.
- In ART-naive patients who are diagnosed with PML, ART should be started immediately **(AII)**.
- In patients who are receiving ART but remains viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression **(AIII)**.

Key to Acronyms: ART = antiretroviral therapy; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

References

1. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: Has the disease outgrown its name? *Ann Neurol*. Aug 2006;60(2):162-173. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16862584.
2. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. Oct 2009;9(10):625-636. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19778765.
3. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog*. Mar 2009;5(3):e1000363. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19325891.
4. Egli A, Infanti L, Dumoulin A, et al. Prevalence of Polyomavirus BK and JC Infection and Replication in 400 Healthy Blood Donors. *J Infect Dis*. Jan 27 2009. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19199540.
5. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. *J Gen Virol*. Jul 2010;91(Pt 7):1849-1853. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20219899.
6. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Annals of neurology*. Sep 2010;68(3):295-303. Available at http://www.ncbi.nlm.nih.gov/pubmed/20737510.
7. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. *J Infect Dis*. Jun 1990;161(6):1128-1133. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2161040.
8. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. *J Infect Dis*. Mar 1994;169(3):485-490. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8158020.
9. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. Jan 15 1999;52(2):253-260. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9932940.
10. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Apr 11 2003;17(6):801-807. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12660526.
11. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. *J Neurovirol*. Aug 2004;10(4):244-249. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15371154.
12. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. *Prog Clin Biol Res*. 1983;105:191-203. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6304757.
13. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J*

Hematol. Dec 2005;80(4):271-281. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16315252.

14. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology*. Oct 12 2010;75(15):1326-1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/20938025.
15. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. Apr 2010;9(4):438-446. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20298967.
16. Molloy ES, Calabrese LH. Therapy: Targeted but not trouble-free: efalizumab and PML. *Nat Rev Rheumatol*. Aug 2009;5(8):418-419. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19648939.
17. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. *Arthritis and rheumatism*. Nov 2010;62(11):3191-3195. Available at http://www.ncbi.nlm.nih.gov/pubmed/20722036.
18. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol*. Aug 2009;10(8):816-824. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19647202.
19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol*. Sep 1 2006;24(25):4123-4128. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16896005.
20. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *Br J Haematol*. Mar 2007;136(5):685-698. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17229246.
21. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol*. Nov 1986;45(6):635-646. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3021914.
22. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. *Am J Pathol*. Sep 1986;124(3):537-558. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2876640.
23. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol (Berl)*. 1989;77(4):379-390. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2540610.
24. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*. Jul 1988;38(7):1060-1065. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3386823.
25. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Annals of neurology*. Mar 2004;55(3):320-328. Available at http://www.ncbi.nlm.nih.gov/pubmed/14991809.
26. Mocroft A, Collaboration AC. OIs, AIDS-Defining Conditions, and HIV-1 Disease Burden. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 27, 2007, 2007; Los Angeles.
27. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *J Infect Dis*. Sep 1999;180(3):621-625. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10438348.
28. Garvey L, Winston A, Walsh J, et al. HIV-associated central nervous system diseases in the recent combination antiretroviral therapy era. *Eur J Neurol*. Mar 2011;18(3):527-534. Available at http://www.ncbi.nlm.nih.gov/pubmed/21159073.
29. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. Sep 1998;44(3):341-349. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9749600.

30. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. *J Neurovirol*. 2003;9 Suppl 1:73-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709876.
31. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9 Suppl 1:25-31. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709868.
32. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *Journal of neurovirology*. Oct 2007;13(5):474-476. Available at http://www.ncbi.nlm.nih.gov/pubmed/17994433.
33. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology*. Jul 1997;49(1):263-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9222204.
34. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. Jan 24 2006;66(2):262-264. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16434670.
35. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. Apr 1997;48(4):836-845. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9109865.
36. Mader I, Herrlinger U, Klose U, Schmidt F, Kuker W. Progressive multifocal leukoencephalopathy: analysis of lesion development with diffusion-weighted MRI. *Neuroradiology*. Oct 2003;45(10):717-721. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12942223.
37. da Pozzo S, Manara R, Tonello S, Carollo C. Conventional and diffusion-weighted MRI in progressive multifocal leukoencephalopathy: new elements for identification and follow-up. *Radiol Med*. Oct 2006;111(7):971-977. Available at http://www.ncbi.nlm.nih.gov/pubmed/17021685.
38. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. Jun 2010;65(6):431-439. Available at http://www.ncbi.nlm.nih.gov/pubmed/20451009.
39. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. Jan 1997;11(1):1-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/9110070.
40. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. Sep 12 2008;22(14):1759-1767. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753934.
41. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Annals of neurology*. Jun 1999;45(6):816-821. Available at http://www.ncbi.nlm.nih.gov/pubmed/10360779.
42. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. Mar 1 2005;40(5):738-744. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15714422.
43. Silver SA, Arthur RR, Erozan YS, Sherman ME, McArthur JC, Uematsu S. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. *Acta Cytol*. Jan-Feb 1995;39(1):35-44. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7847007.
44. Jochum W, Weber T, Frye S, Hunsmann G, Luke W, Aguzzi A. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. *Acta Neuropathol (Berl)*. Sep 1997;94(3):226-231. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9292691.

45. Knowles WA, Luxton RW, Hand JF, Gardner SD, Brown DW. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leucoencephalopathy. *Clin Diagn Virol*. Aug 1995;4(2):183-194. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15566839.

46. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol*. 2006;577:19-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/16626025.

47. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. Aug 7 2008. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18688812.

48. Tan CS, Ellis LC, Wuthrich C, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J Virol*. Sep 2010;84(18):9200-9209. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20610709.

49. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47-53. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709872.

50. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology*. Feb 1999;52(3):623-625. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10025799.

51. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *J Neurovirol*. Aug 1999;5(4):421-429. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10463864.

52. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS*. Oct 1 1999;13(14):1881-1887. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10513646.

53. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *Journal of neurovirology*. Aug 2001;7(4):358-363. Available at http://www.ncbi.nlm.nih.gov/pubmed/11517417.

54. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. Sep 6 2002;16(13):1791-1797. Available at http://www.ncbi.nlm.nih.gov/pubmed/12218391.

55. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis*. Apr 15 2003;36(8):1047-1052. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12684918.

56. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. Aug 14 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20710013.

57. Pazzi A, Galli L, Costenaro P, et al. The Relationship between Outcome of Progressive Multifocal Leukoencephalopathy and Type and Response to ART in Previously HAART-untreated Patients. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007, 2007; Los Angeles.

58. Gasnault J, Hendel Chavez E, Dorofeev E, et al. Acceleration of immune recovery on intensified ART improves survival in patients with AIDS-related PML : preliminary reports of the ANRS 125 Trial. Paper presented at: CROI 20072007; Los Angeles, CA.

59. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. Jan 2008;65(1):65-70. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18195140.

60. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology*. Feb 15 2011;76(7):644-651. Available at http://www.ncbi.nlm.nih.gov/pubmed/21248274.

61. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med*. May 7 1998;338(19):1345-1351. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9571254.

62. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol*. Aug 2001;7(4):375-381. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11517420.

63. Jiang ZG, Cohen J, Marshall LJ, Major EO. Hexadecyloxypropyl-cidofovir (CMX001) suppresses JC virus replication in human fetal brain SVG cell cultures. *Antimicrob Agents Chemother*. Nov 2010;54(11):4723-4732. Available at http://www.ncbi.nlm.nih.gov/pubmed/20823288.

64. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. Nov 19 2004;306(5700):1380-1383. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15550673.

65. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. Mar 2008;132(1-2):97-103. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18093678.

66. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone [correction of zisprasidone], risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. *Med Hypotheses*. 2005;65(3):585-586. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16004936.

67. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. *Science*. Jul 15 2005;309(5733):381-382. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16020715.

68. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: A clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res*. Nov 27 2006. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17140673.

69. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. Sep 2006;77(9):1079-1082. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16914758.

70. Lanzafame M, Ferrari S, Lattuada E, et al. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy. *Infez Med*. Mar 2009;17(1):35-37. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19359824.

71. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. Feb 2009;66(2):255-258. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19204164.

72. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology*. Oct 1993;196(2):612-618. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8396804.

73. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. Jun 2003;9(3):411-419. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12775425.

74. Clifford D, Nath A, Cinque P, et al. Mefloquine Treatment in Patients with Progressive Multifocal Leukoencephalopathy. *Neurology*. 2011;76:A28.

75. Huang SS, Skolasky RL, Dal Pan GJ, Royal W, 3rd, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. Jun 1998;4(3):324-332. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9639075.

76. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for

therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. Aug 2001;7(4):353-357. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11517416.

77. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. *Neurology*. Jan 10 2006;66(1):149-150. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16401874.
78. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant*. Dec 1997;20(11):983-987. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9422479.
79. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. *Ann Hematol*. Jul 2002;81(7):410-413. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12185517.
80. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology*. Nov 8 2005;65(9):1510. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16275856.
81. Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol (Berl)*. Apr 2005;109(4):449-455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15739098.
82. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. Apr 28 2009;72(17):1458-1464. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19129505.
83. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS*. Sep 28 2001;15(14):1900-1902. Available at http://www.ncbi.nlm.nih.gov/pubmed/11579261.
84. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. Nov 15 2002;35(10):1250-1257. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12410486.
85. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. Aug 2003;74(8):1142-1144. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12876257.
86. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? *Neurology*. Dec 28 2004;63(12):2452-2453. Available at http://www.ncbi.nlm.nih.gov/pubmed/15623736.
87. Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R, De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. *J Clin Microbiol*. Aug 2005;43(8):4175-4177. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16081969.
88. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology*. Feb 3 2009;72(5):402-409. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19188571.
89. Ransohoff RM. PML risk and natalizumab: more questions than answers. *Lancet Neurol*. Mar 2010;9(3):231-233. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20117056.
90. Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS*. Nov 27 2009;23(18):2545-2546. Available at http://www.ncbi.nlm.nih.gov/pubmed/19907215.

Malaria (Last updated March 28, 2017; last reviewed March 28, 2017)

Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. In 2015, the World Health Organization estimated that 97 countries had ongoing malaria transmission, and almost half the world's population, approximately 3.2 billion people, lived in areas with some risk of malaria transmission.1 Of the nearly 214 million cases of malaria worldwide in 2015 (based on reports and models), approximately 88% (188 million) occurred in Africa, the area of the world with the highest HIV prevalence.[1] Approximately 438,000 deaths were attributable to malaria in 2015, with ~90% occurring in Africa and 74% of those deaths in children younger than 5 years of age. Fifteen countries, mainly in sub-Saharan Africa, account for 80% of malaria cases and 78% of deaths worldwide.[1] Current attributable morbidity and mortality are likely underestimated, given our limited understanding, surveillance, and reporting of non-falciparum infections.

Malaria typically is transmitted by the bite of an infected female *Anopheles sp.* mosquito. Reports of vertical transmission and infection after blood transfusion do exist, but these routes of transmission are uncommon in non-endemic areas.[2-5]

Malaria in humans can be caused by any one of five species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* (a zoonotic species that also infects macaques in Southeast Asia).[5] Although *P. vivax* infections are more common and occur in a far wider geographic distribution,[6] *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections. *P. vivax*, however, should not be discounted as a risk for travelers in many parts of the world.

Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given this substantial overlap, even modest interactions between them have public health importance.[7,8] Malaria influences the natural history of HIV infection, and HIV infection alters the natural history and severity of malaria.[9]

Many foreign-born individuals develop malaria in the United States because of distant exposure before their arrival, or as a result of more recent travel for business or family reasons. Similarly, U.S.-born individuals can develop malaria during travel to endemic areas.[10-13] Failure to take appropriate chemoprophylaxis is a common problem for both groups of individuals.[14,15] People who formerly lived in malarious areas may believe that they are immune, and therefore do not need to take prophylaxis.[16] Such patients are at high risk of infection, however, because they likely have lost partial immunity within 6 months after leaving endemic regions.

Consideration of malaria in returning travelers who are febrile is important: Of the nearly 50 million individuals who travel to developing countries each year, between 5% and 11% develop a fever during or after travel.[17-20] Malaria is a surprisingly common cause of these fevers.[21]

Clinical Manifestations

The clinical syndromes caused by *Plasmodium* species depend on prior exposure.[22] While many native U.S. travelers have no prior immunity, clinical manifestations in those who have resided in malarious areas depend on whether they lived in an area with stable endemic malaria transmission (year round) or unstable (seasonal, infrequent or very low) transmission.[23]

In stable endemic areas, children younger than age 5 years may experience chronic infections with recurrent parasitemia, resulting in severe anemia and death. Children who survive these infections usually acquire partial immunity by age 5 years, and if they remain in the area where malaria is endemic, they maintain this immunity into adulthood. In stable endemic areas, adults usually experience asymptomatic or milder infections as a result of this acquired immune response. However, as noted previously, patients who leave endemic areas and subsequently return may be at high risk of disease because they likely have lost partial

immunity 6 months after leaving endemic regions.

In unstable transmission areas, protective immunity is not acquired. For populations in these areas, the overwhelming clinical manifestation is acute febrile disease that can be complicated by cerebral malaria, affecting persons of all ages.

When pregnant women in areas of unstable transmission develop acute malaria, the consequences may include spontaneous abortion and stillbirth. In more stable transmission areas, pregnant women, particularly primigravidas, may lose some acquired immunity. Although infections may continue to be asymptomatic, infected pregnant women may acquire placental malaria that contributes to intrauterine growth retardation, low birth weight, and increased infant mortality.

Patients with malaria can exhibit various symptoms and a broad spectrum of severity, depending upon factors such as the infecting species and level of acquired immunity in the host. HIV-immunosuppressed patients in endemic areas may lose acquired malarial immunity, and HIV-immunosuppressed adults with little or no previous malaria exposure (such as travelers) appear to be at increased risk of severe outcomes.[24]

The incubation period for *P. falciparum* is from a week to several months, but most often less than 60 days. Patients can present much later (>1 year), but this pattern is more common with other species, especially *P. vivax*. In non-immune patients, typical symptoms of malaria include fever, chills, myalgias and arthralgias, headache, diarrhea, vomiting, and other non-specific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also may be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* malaria; those with *P. malariae* occur every 72 hours. This classic presentation is highly variable, however, and may not be present. *P. knowlesi*, known to cause human infection in Southeast Asia in travelers to jungle/forested areas, is clinically indistinguishable from other species of malaria, and the overwhelming majority of patients present with uncomplicated disease (~90%).[25]

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with central nervous system symptoms can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in patients infected with *P. falciparum*; in Africa, case fatality rates with cerebral malaria approach 40%.[26-28] The risk of severe and complicated illness is increased in patients with high levels of parasitemia and without partial immunity. Metabolic acidosis is an important manifestation of severe malaria and an indicator of poor prognosis.[29] Other acute complications include renal failure, hypoglycemia, disseminated intravascular coagulation, shock, and acute pulmonary edema.[30] *P. falciparum* is the species most commonly responsible for severe disease and death, although the other species can cause severe disease and death as well.[25,31]

Effect of HIV on Parasitemia and Clinical Severity

HIV infection impairs acquired immunity to malaria that is present in older children and adults in stable endemic areas. Large cohort studies have demonstrated the increased frequency (with rates one- to two-fold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher-density parasitemia associated with more advanced immunosuppression, particularly among those with CD4 T-lymphocyte (CD4) cell counts <350 cells/mm^3.[32-34] Increased rates of malaria among individuals with HIV do not appear to be as great as the rates observed with classic opportunistic infections such as tuberculosis and *Pneumocystis jirovecii* pneumonia.[35]

In a prospective cohort study in an area with unstable malaria transmission, HIV-infected non-immune adults were found to be at increased risk of severe malaria, and the risk was associated with a low CD4 cell count.[36] Non-immune HIV-infected patients were substantially more likely to have severe clinical malaria than were non-immune patients without HIV. In KwaZulu Natal, an area of unstable malaria transmission, HIV-infected adults hospitalized for malaria were substantially more likely to die or require an intensive care unit admission than those who were not HIV-infected.[37] In contrast, HIV infection did not confer an increased risk of poor outcomes among partially immune adults in areas with more stable transmission.[32] In a cross-sectional

study of travelers returning to France from malaria-endemic areas between 2000 and 2003, HIV-infected individuals with CD4 counts <350 cells/mm^3 were at significantly higher risk of developing severe malaria, compared with those who were HIV-negative.[34]

Effects of Malaria on Mother-to-Child HIV Transmission

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages38 and increased viral load,[39] raising the possibility of placental malaria leading to increased mother-to-child transmission (MTCT) of HIV. In addition, fetal immune activation by malaria antigens may increase susceptibility to HIV infection.[40] Data are conflicting concerning the effect of malaria during pregnancy on risk of MTCT in the pre-ART era and are limited since the widespread use of antiretroviral therapy (ART) for prevention of MTCT.[41-43]

Diagnosis

A malaria diagnosis must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from individuals who have been to such areas.

Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, polymerase chain reaction-based assays, and serologic tests, though serologic tests which detect host antibody are inappropriate for the diagnosis of acute malaria.

Direct microscopic examination of intracellular parasites on stained blood films is the standard for definitive diagnosis in nearly all settings because it allows for identification of the species and provides a measure of parasite density. Microscopic diagnosis of *P. knowlesi* is difficult because it is commonly misidentified as *P. malariae*, which tends to follow a more benign course. Providers should have a high index of suspicion for *P. knowlesi* in travelers returning from Southeast Asia.[31]

In non-immune patients with all types of malaria, symptoms may develop before detectable levels of parasitemia are evident. For this reason, several blood smear examinations taken at 12– to 24-hour intervals may be needed to positively rule out a diagnosis of malaria in symptomatic patients. Guidelines for laboratory diagnosis are summarized elsewhere and are available at the Centers for Disease Control and Prevention (CDC)'s malaria website (https://www.cdc.gov/malaria). Rapid diagnostic tests, particularly for the diagnosis of *P. falciparum*, can be used depending on the local expertise and practice and can facilitate prompt diagnosis and treatment of infected patients, but must be followed by microscopy.

Preventing Exposure

Pre-travel evaluation by a travel medicine specialist can provide specific education about risk of exposure in various geographic locales, the utility of insecticide-impregnated bed nets in the setting where the individual will be traveling or residing, and the use of DEET (N,N-diethyl-3-methyl-benzamide)-containing repellants.

Infection with *P. falciparum* can be more severe in HIV-infected patients with low CD4 cell counts and in pregnant women regardless of HIV infection than in other individuals. Because no chemoprophylactic regimen is completely effective, HIV-infected patients with low CD4 cell counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible **(AIII)**. If travel to an endemic area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

For United States travelers (including HIV-infected patients) to endemic areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. Recommendations for prophylaxis are the same for HIV-infected patients as for those who are not HIV-

infected and are available at CDC's malaria website **(AIII)** (https://www.cdc.gov/malaria).

Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.[44] A recent study of HIV-infected patients in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, and then reduced another 50% when antiretroviral (ARV) drugs were provided, and finally reduced another 50% with provision of insecticide-treated nets.[45] However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the recommended antimalarials. Therefore, HIV-infected travelers should not rely on prophylaxis with cotrimoxazole for chemoprophylaxis against malaria **(AIII)**.

Treating Disease

Because *P. falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment **(AIII)**. Diagnosis prior to treatment should always be pursued; however, treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed **(AIII)**.

Choice of treatment is guided by the degree of parasitemia, the species of *Plasmodium*, a patient's clinical status, and the likely drug susceptibility of the infecting species (as determined by where the infection was acquired).

For HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients **(AIII)**. CDC posts current treatment recommendations on its website (https://www.cdc.gov/malaria) and has clinicians on call 24 hours to provide advice to clinicians on diagnosing and treating malaria (CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours).

Special Considerations with Regard to Starting ART

There is no reason to defer ART initiation after patients have recovered from acute malaria.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Careful monitoring of patients (especially those with *P. falciparum* malaria) is necessary, including measurement of peripheral parasitemia and hemoglobin and blood glucose levels, as well as assessment of cerebral, pulmonary, and renal function. Frequency of monitoring depends on severity of disease, a patient's immune status, and the species of *Plasmodium*.

Chemoprophylaxis or treatment for malaria in patients receiving ARV agents requires attention to potential drug interactions. Several potential drug interactions can occur between antimalarial and HIV drugs as well as other medications used to treat HIV-associated opportunistic infections (see Table 5).[46] Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at http://www.hiv-druginteractions.org. Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Insufficient data are available to suggest that dose adjustments are needed.

Quinine levels may be increased by ritonavir-containing regimens or cobicistat; conversely, nevirapine and efavirenz can reduce plasma quinine levels. Potential interactions can occur between ritonavir or cobicistat and chloroquine, but their clinical significance is unclear, and until further data are available, no dose adjustments are recommended.

Artemether-lumefantrine is now approved in the United States for treatment of uncomplicated *P. falciparum* infection. Data in children suggest that this combination is well tolerated and safe in HIV-infected children,[47] however, efficacy data are conflicting in HIV-infected adults. An open-label trial in Tanzania demonstrated

excellent efficacy (97.6%) of artemether-lumefantrine for treating uncomplicated *P. falciparum* malaria in HIV-infected adults on nevirapine-based ART.[48] Conversely, 28-day clinical and parasitologic response was sub-optimal in the efavirenz-based ART group, with efficacy of 82.5%, and a 19-fold increased risk of recurrent parasitemia compared to the control group of HIV-infected adults not on ART.[48] Artesunate is available for treatment of severe malaria through a compassionate use Investigational New Drug application. A trial in Uganda demonstrated the effectiveness of artesunate plus amodiaquine in HIV-infected children, but treatment was associated with increased risk of neutropenia in those on ART, particularly zidovudine, which was attributed to the amodiaquine component of therapy.[49]

Ritonavir or cobicistat-boosed ARV regimens and non-nucleoside reverse transcriptase inhibitors have the potential to affect metabolism of artemisinin-containing drugs,[50] but the overall effect and clinical significance remain unclear. No dose alterations currently are recommended.

No immune reconstitution inflammatory syndrome (IRIS) has been described in association with malaria.

Managing Treatment Failure

HIV-infected individuals are at increased risk of malaria treatment failure.[51] Management of treatment failure is the same in HIV-infected and HIV-uninfected patients, except for considerations about drug interactions between ART and antimalarial drugs. Drug-resistant malaria and possible concomitant infections should be considered in HIV-infected patients whose malaria fails to respond to therapy.

Preventing Recurrence

If the species of malaria identified is *P. vivax* or *P. ovale*, which can cause recurrence due to hepatic phase of infection, then treatment with primaquine in addition to standard treatment is recommended to prevent recurrence **(AI)**. Guidelines for primaquine treatment do not differ in HIV-infected individuals.

Special Considerations During Pregnancy

Malaria in pregnancy affects both mother and fetus. Infection with *P. falciparum* during pregnancy can increase maternal risk of severe disease and anemia and risk for stillbirth, preterm birth, and low birth weight.[52] The diagnosis of malaria in pregnant women is the same as in women who are not pregnant.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended.[53] For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with mefloquine for 7 days is recommended. For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with mefloquine or quinine and clindamycin is recommended as per CDC guidelines.[54]

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk of birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe.[53,55] Because of the potential for hypoglycemia, glucose levels should be monitored in pregnant women treated with quinine and their neonates. Clindamycin use has not been associated with birth defects. Animal and human data on use of prophylactic and treatment doses of mefloquine do not suggest teratogenicity and the drug can be used safely during all trimesters.[56] One randomized trial of mefloquine used in addition to daily cotrimoxazole for malaria prophylaxis in pregnant women living with HIV demonstrated an increased risk of transmission of HIV to the infant in the mefloquine arm, potentially because of drug interactions.[57] Although experience is limited, available data on artemether-lumefantrine during pregnancy suggest that use is not associated with increased adverse events or birth defects.[58] A pharmacokinetic study in HIV-uninfected persons found no difference in levels between pregnant and non-pregnant subjects except for small

differences in elimination half-life of lumefantrine.[59] Data on pharmacokinetics in HIV-infected pregnant women were not included. Because of limited data, atovaquone-proguanil is not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin, quinine monotherapy, or mefloquine are unavailable or not tolerated.[55] Tetracyclines are not recommended in pregnancy because of increased risk of maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal glucose-6-phosphate dehydrogenase (G6PD) deficiency. After treatment, all pregnant women with *P. vivax* and *P. ovale* should receive chloroquine prophylaxis for the duration of pregnancy to avoid relapses. Once-weekly mefloquine can be used for prophylaxis in pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains. Women who have normal G6PD screening tests can be treated with primaquine after delivery.

Recommendations for Preventing and Treating Malaria

Preventing Malaria in Patients Traveling to Endemic Areas:
• Recommendations are the same for HIV-infected and HIV-uninfected patients.
• Specific recommendations are based on region of travel, malaria risks, and drug susceptibility in the region.
• Clinicians should refer to the following website for the most up-to-date recommendations: https://www.cdc.gov/malaria
• TMP-SMX has been shown to reduce malaria in HIV-infected adults in Africa. However, it is not as effective as antimalarial prophylactic regimens. Therefore, HIV-infected travelers **should not** rely on TMP-SMX for prophylaxis against malaria **(AIII)**.
Treating Malaria
• Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infection should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to therapy **(AIII)**.
• When suspicion of malaria is low, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations.
• Treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed **(AIII)**.
• When malaria is strongly suspected, but not yet confirmed, clinicians are advised to consider and initiate treatment for other possible diagnoses in addition to malaria.
• Treatment recommendations for HIV-infected patients are the same as HIV-uninfected patients **(AIII)**.
• Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, and the likely drug susceptibility of the infected species.
• For treatment recommendations for specific region, clinicians should refer to
o The CDC malaria website: https://www.cdc.gov/malaria
o The CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours.

Key to Acronyms: CDC = the Centers for Disease Control and Prevention; TMP-SMX = Trimethoprim-sulfamethoxazole

References

1. World Health Organization. World Malaria Report 2015. 2015. Available at http://www.who.int/malaria/publications/world-malaria-report-2015/en/.
2. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*. Jun 28 2001;344(26):1973-1978. Available at http://www.ncbi.nlm.nih.gov/pubmed/11430326.
3. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. *JAMA*. Jul 22-29 1992;268(4):516-519. Available at http://www.ncbi.nlm.nih.gov/pubmed/1619744.
4. Centers for Disease C. Update: self-induced malaria associated with malariotherapy for Lyme disease -Texas. *MMWR Morb Mortal Wkly Rep*. Oct 4 1991;40(39):665-666. Available at http://www.ncbi.nlm.nih.gov/pubmed/1896006.
5. Mali S, Steele S, Slutsker L, Arguin PM, Centers for Disease C, Prevention. Malaria surveillance - United States, 2008. *MMWR Surveill Summ*. Jun 25 2010;59(7):1-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/20577158.
6. Guerra CA, Howes RE, Patil AP, et al. The international limits and population at risk of Plasmodium vivax transmission

in 2009. *PLoS Negl Trop Dis*. 2010;4(8):e774. Available at http://www.ncbi.nlm.nih.gov/pubmed/20689816.

7. Korenromp EL, Williams BG, de Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis*. Sep 2005;11(9):1410-1419. Available at http://www.ncbi.nlm.nih.gov/pubmed/16229771.
8. Van Geertruyden JP, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. *Malar J*. 2008;7:134. Available at http://www.ncbi.nlm.nih.gov/pubmed/18647387.
9. Slutsker L, Marston BJ. HIV and malaria: interactions and implications. *Curr Opin Infect Dis*. Feb 2007;20(1):3-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/17197875.
10. Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of Travel of Adults Infected with HIV. *J Travel Med*. Jun 1 1995;2(2):85-88. Available at http://www.ncbi.nlm.nih.gov/pubmed/9815367.
11. Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel Med*. Jun 1999;6(2):71-75. Available at http://www.ncbi.nlm.nih.gov/pubmed/10381957.
12. Castelli F, Patroni A. The human immunodeficiency virus-infected traveler. *Clin Infect Dis*. Dec 2000;31(6):1403-1408. Available at http://www.ncbi.nlm.nih.gov/pubmed/11096010.
13. Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. *Am J Med*. Jul 2007;120(7):574-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/17602926.
14. Smego RA, Jr. Effectiveness of antimalarial drugs. *N Engl J Med*. Jul 28 2005;353(4):420-422; author reply 420-422. Available at http://www.ncbi.nlm.nih.gov/pubmed/16050053.
15. Suh KN, Mileno MD. Challenging scenarios in a travel clinic: advising the complex traveler. *Infect Dis Clin North Am*. Mar 2005;19(1):15-47. Available at http://www.ncbi.nlm.nih.gov/pubmed/15701545.
16. Sherrard AW, McCarthy AE. Travel patterns and health risks for patients infected with HIV. *Travel Med Infect Dis*. Sep 2009;7(5):291-295. Available at http://www.ncbi.nlm.nih.gov/pubmed/19747664.
17. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med*. Aug 15 2002;347(7):505-516. Available at http://www.ncbi.nlm.nih.gov/pubmed/12181406.
18. Spira AM. Assessment of travellers who return home ill. *Lancet*. Apr 26 2003;361(9367):1459-1469. Available at http://www.ncbi.nlm.nih.gov/pubmed/12727414.
19. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis*. Jul 1987;156(1):84-91. Available at http://www.ncbi.nlm.nih.gov/pubmed/3598228.
20. Winer L, Alkan M. Incidence and precipitating factors of morbidity among Israeli travelers abroad. *J Travel Med*. Sep-Oct 2002;9(5):227-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/12962594.
21. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis*. Jun 15 2007;44(12):1560-1568. Available at http://www.ncbi.nlm.nih.gov/pubmed/17516399.
22. Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. *Science*. May 14 2010;328(5980):866-871. Available at http://www.ncbi.nlm.nih.gov/pubmed/20466925.
23. Snow RW, Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa. *Adv Parasitol*. 2002;52:235-264. Available at http://www.ncbi.nlm.nih.gov/pubmed/12521262.
24. Matteelli A, Casalini C, Bussi G, et al. Imported malaria in an HIV-positive traveler: a case report with a fatal outcome. *J Travel Med*. Jul-Aug 2005;12(4):222-224. Available at http://www.ncbi.nlm.nih.gov/pubmed/16086898.
25. Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and laboratory features of human Plasmodium knowlesi infection. *Clin Infect Dis*. Sep 15 2009;49(6):852-860. Available at http://www.ncbi.nlm.nih.gov/pubmed/19635025.
26. Severe and complicated malaria. World Health Organization, Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg*. 1990;84 Suppl 2(Suppl 2):1-65. Available at http://www.ncbi.nlm.nih.gov/pubmed/2219249.
27. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bull World Health Organ*. 1989;67(2):189-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/2743538.
28. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med*. May 1989;71(265):441-459. Available at http://www.ncbi.nlm.nih.gov/pubmed/2690177.
29. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. *QJM*. Apr 1997;90(4):263-270.

Available at http://www.ncbi.nlm.nih.gov/pubmed/9307760.

30. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. May 25 1995;332(21):1399-1404. Available at http://www.ncbi.nlm.nih.gov/pubmed/7723795.
31. Cox-Singh J, Davis TM, Lee KS, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. Jan 15 2008;46(2):165-171. Available at http://www.ncbi.nlm.nih.gov/pubmed/18171245.
32. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet*. Sep 23 2000;356(9235):1051-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/11009139.
33. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis*. Sep 15 2005;192(6):984-991. Available at http://www.ncbi.nlm.nih.gov/pubmed/16107950.
34. Mouala C, Guiguet M, Houze S, et al. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS*. Sep 24 2009;23(15):1997-2004. Available at http://www.ncbi.nlm.nih.gov/pubmed/19654499.
35. Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. *J Infect Dis*. Mar 15 2006;193(6):872-878. Available at http://www.ncbi.nlm.nih.gov/pubmed/16479522.
36. Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis*. Dec 1 2005;41(11):1631-1637. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267737.
37. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS*. Feb 20 2004;18(3):547-554. Available at http://www.ncbi.nlm.nih.gov/pubmed/15090809.
38. Tkachuk AN, Moormann AM, Poore JA, et al. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. *J Infect Dis*. Mar 15 2001;183(6):967-972. Available at http://www.ncbi.nlm.nih.gov/pubmed/11237815.
39. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS*. Apr 30 2004;18(7):1051-1059. Available at http://www.ncbi.nlm.nih.gov/pubmed/15096809.
40. Steiner K, Myrie L, Malhotra I, et al. Fetal immune activation to malaria antigens enhances susceptibility to in vitro HIV infection in cord blood mononuclear cells. *J Infect Dis*. Sep 15 2010;202(6):899-907. Available at http://www.ncbi.nlm.nih.gov/pubmed/20687848.
41. Msamanga GI, Taha TE, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. *Am J Trop Med Hyg*. Apr 2009;80(4):508-515. Available at http://www.ncbi.nlm.nih.gov/pubmed/19346367.
42. Bulterys PL, Chao A, Dalai SC, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. *Am J Trop Med Hyg*. Aug 2011;85(2):202-206. Available at http://www.ncbi.nlm.nih.gov/pubmed/21813835.
43. Ezeamama AE, Duggan C, Manji KP, et al. Clinical malaria diagnosis in pregnancy in relation to early perinatal mother-to-child transmission of HIV: a prospective cohort study. *HIV Med*. May 2014;15(5):276-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/24215465.
44. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at http://www.ncbi.nlm.nih.gov/pubmed/10232311.
45. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet*. Apr 15 2006;367(9518):1256-1261. Available at http://www.ncbi.nlm.nih.gov/pubmed/16631881.
46. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS*. Jul 1 2005;19(10):995-1005. Available at http://www.ncbi.nlm.nih.gov/pubmed/15958830.
47. Katrak S, Gasasira A, Arinaitwe E, et al. Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperaquine for malaria in young HIV-infected and uninfected children. *Malar J*. 2009;8:272. Available at http://www.

ncbi.nlm.nih.gov/pubmed/19948038.

48. Maganda BA, Minzi OM, Kamuhabwa AA, Ngasala B, Sasi PG. Outcome of artemether-lumefantrine treatment for uncomplicated malaria in HIV-infected adult patients on anti-retroviral therapy. *Malar J*. May 30 2014;13:205. Available at http://www.ncbi.nlm.nih.gov/pubmed/24885714.
49. Gasasira AF, Kamya MR, Achan J, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. Apr 1 2008;46(7):985-991. Available at http://www.ncbi.nlm.nih.gov/pubmed/18444813.
50. Parikh S, Gut J, Istvan E, Goldberg DE, Havlir DV, Rosenthal PJ. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrob Agents Chemother*. Jul 2005;49(7):2983-2985. Available at http://www.ncbi.nlm.nih.gov/pubmed/15980379.
51. Van Geertruyden JP, Mulenga M, Mwananyanda L, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. *J Infect Dis*. Oct 1 2006;194(7):917-925. Available at http://www.ncbi.nlm.nih.gov/pubmed/16960779.
52. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. Feb 2007;7(2):93-104. Available at http://www.ncbi.nlm.nih.gov/pubmed/17251080.
53. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment of malaria in the United States: a systematic review. *JAMA*. May 23 2007;297(20):2264-2277. Available at http://www.ncbi.nlm.nih.gov/pubmed/17519416.
54. Centers for Disease Control and Prevention. Part 3: Alternatives for Pregnant Women and Treatment of Severe Malaria. Treatment of Malaria: Guidelines For Clinicians (United States) 2013. Available at https://www.cdc.gov/malaria/diagnosis_treatment/clinicians3.html.
55. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. *Trans R Soc Trop Med Hyg*. Mar-Apr 2002;96(2):180-184. Available at http://www.ncbi.nlm.nih.gov/pubmed/12055810.
56. Centers for Disease Control and Prevention. Update: New Recommendations for Mefloquine Use in Pregnancy. 2011; Available at http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html.
57. Gonzalez R, Desai M, Macete E, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Med*. Sep 2014;11(9):e1001735. Available at http://www.ncbi.nlm.nih.gov/pubmed/25247995.
58. Manyando C, Kayentao K, D'Alessandro U, Okafor HU, Juma E, Hamed K. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria during pregnancy. *Malar J*. May 01 2012;11:141. Available at http://www.ncbi.nlm.nih.gov/pubmed/22548983.
59. Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-Lumefantrine Pharmacokinetics and Clinical Response Are Minimally Altered in Pregnant Ugandan Women Treated for Uncomplicated Falciparum Malaria. *Antimicrob Agents Chemother*. Dec 14 2015;60(3):1274-1282. Available at http://www.ncbi.nlm.nih.gov/pubmed/26666942.

Penicilliosis marneffei (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.[1-3] More recently, indigenous cases of penicilliosis have been seen in several states of India, particularly Manipur, which is a new endemic area for this fungus.[4-6]

Before the era of antiretroviral therapy (ART), penicilliosis was the presenting AIDS-defining illness in 6.8% of HIV-infected patients from the northern provinces of Thailand and less common elsewhere.[7] Most cases of penicilliosis are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3.[8] The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered.[9]

No data are available on acquisition and transmission of penicilliosis. However, like histoplasmosis, it is believed to be acquired by inhalation of microconidia from the mycelial phase of the organism. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and it is the presumed mechanism for disease occurrence in nonendemic areas. Evidence exists for seasonality in penicilliosis infections; increased cases have been noted during the rainy months.[10,11]

Clinical Manifestations

The common clinical manifestations include fever, anemia, weight loss, and generalized skin papules with central umbilication resembling molluscum contagiosum.[1,5] Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs, such as the central nervous system, bone marrow, lymph node, lung, liver, and intestine, has been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels.[3]

Diagnosis

The definitive diagnosis of penicilliosis is based on isolation of organisms from cultures of blood or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. *P. marneffei* exibits dimorphic growth in culture. At 25°C, the fungus grows as a mold, demonstrating characteristic colonies that include a flat green surface and underlying deep red coloring. At 37°C the fungus grows as white colonies of yeast.[12]

An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffei*.[1,5] In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.[13]

Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting endemic areas, and particularly rural areas in those regions **(BIII)**.

Preventing Disease

A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole, 200 mg daily for primary prophylaxis, significantly reduced occurrence of systemic fungal infections (cryptococcosis and penicilliosis) in HIV-infected patients with CD4 counts <200 cells/mm^3.[8] Fluconazole

may also be effective prophylaxis.[14] For most patients from the United States, such primary prophylaxis would only be indicated in unusual situations in which those who are highly immunosuppressed have to travel to high-risk areas.

Indication for Primary Prophylaxis

All HIV-infected patients with CD4 counts <100 cells/mm^3 who reside or stay for a long period in northern Thailand, Vietnam, and southern China, and particularly in rural areas, should be administered primary prophylaxis **(BI)**. The preferred drug for prophylaxis is oral itraconazole, 200 mg/day **(BI)**. An alternative drug is oral fluconazole 400 mg once weekly **(BII)**. Primary prophylaxis is not indicated in other geographic areas.[15]

Discontinuation of Primary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of primary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse in penicilliosis and invasive fungal infections after discontinuation of itraconazole in patients receiving ART who had CD4 counts >100 cells/mm^3.[16] Therefore, primary prophylaxis for penicilliosis can logically be discontinued in AIDS patients who receive combination ART and have CD4 counts >100 cells/mm^3 for ≥6 months but there are no convincing data addressing this issue **(CII)**. Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(BIII)**.

Treating Disease

The recommended treatment is liposomal amphotericin B, 3 to 5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks **(AII)**, followed by secondary prophylaxis.[17] Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks **(BII)**,[18] followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal. Itraconazole oral solution can be taken on an empty stomach.

The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks **(BII)**.[19] The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.

Special Considerations with Regard to Starting ART

No studies exist regarding the optimal time to start ART in HIV-infected patients with acute penicilliosis, but anecdotal experience and information from clinical trials on other HIV associated opportunistic infections suggests that in those with active penicilliosis who have CD4 counts ≤50 cells/mm^3, ART should be started as soon as possible after the initiation of antifungal therapy **(BIII)**. In patients with CD4 counts >50 cells/mm^3, it may be prudent to delay initiation of ART until after completion of the first 2 weeks of induction therapy for penicilliosis **(CIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline reduces the risk of nephrotoxicity during treatment **(BII)**. Infusion-related adverse reactions can be ameliorated by pretreatment with acetaminophen and diphenhydramine.

Because absorption of itraconazole can be erratic and because itraconazole can interact with some antiretroviral drugs, serum itraconazole levels should be obtained in all patients to ensure adequate drug exposure **(AIII)**. The serum concentration should be >1 µg/mL. Itraconazole solution is recommended over the capsule formulation because of better bioavailability, but this has not been studied specifically in AIDS patients.

Azoles and antiretroviral drugs such as protease ihibitors (PIs) and non-nucleoside reverse transciptase inhibitors (NNRTIs) do interact (see Table 5). Through the CYP3A4 mechanism, itraconazole and voriconazole can increase blood levels and effects of PIs and NNRTIs. On the other hand, NNRTIs can slightly decrease blood levels of itraconazole and voriconazole. Close monitoring should be done when using these drugs together.

The unmasking type of immune reconstitution inflammatory syndrome (IRIS) has been reported in several patients with penicilliosis.[20,21] No paradoxical IRIS responses have been reported when ART is initiated in patients with established penicilliosis. ART should not be withheld because of concern for possible development of IRIS **(AIII)**.

Managing Treatment Failure

Voriconazole has been reported to have good outcomes and can be used in patients whose infections fail to respond to initial therapy with amphotericin B followed by itraconazole **(BII)**.[19]

Preventing Recurrence

When To Start Secondary Prophylaxis

A study showed that more than 50% of patients not treated with ART had relapse of *P. marneffei* within 6 months after discontinuation of antifungal therapy.[18,22] A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients, reduced the relapse rate for *P. marneffei* from 57% to 0% ($P < 0.001$).[22] All patients who successfully complete treatment for penicilliosis should receive secondary prophylaxis (chronic maintenance therapy) with oral itraconazole 200 mg/day **(AI)** and should be started on ART if that was not done during acute disease **(AIII)**.

When To Stop Secondary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse of penicilliosis after discontinuation of itraconazole in patients receiving ART whose CD4 cell counts were >100 cells/mm^3.[16] Therefore, secondary prophylaxis for penicilliosis can be discontinued in AIDS patients who receive combination ART and have CD4 cell counts >100 cells/mm^3 for at least 6 months **(BII)**. Secondary prophylaxis should be reintroduced if the CD4 cell count decreases to <100 cells/mm^3 **(AIII)**

Special Considerations During Pregnancy

Diagnosis and treatment of penicilliosis during pregnancy are similar to those in non-pregnant adults, with the following considerations regarding antifungal use in pregnancy. Amphotericin B has not been shown to be teratogenic in animals, and no increase in anomalies has been seen with its use in humans. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so the data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited. Voriconazole is Food and Drug Administration category D because of cleft palate and renal defects seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended. No evidence of birth defects has been seen after episodic exposure to single, 150-mg doses of fluconazole. With chronic use of doses ≥400 mg in pregnancy, however, 5 cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported (fluconazole embryopathy).[23]

Substitution of amphotericin B for high-dose azoles in the first trimester is recommended **(BIII)**. Women on secondary prophylaxis with itraconazole or other azoles should postpone pregnancy until their CD4 cell counts have been restored with ART, such that prophylaxis can be discontinued **(BIII)**.

Recommendations for Preventing and Treating *Penicillium marneffei* Infection

Preventing 1st Episode of Penicilliosis (Primary Prophylaxis)

Indication for Primary Prophylaxis:

- Patients with CD4 count <100 cells/mm^3 who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas **(BI)**

Preferred Therapy:

- Itraconazole[a] 200 mg PO once daily **(BI)**

Alternative Therapy:

- Fluconazole 400 mg PO once weekly **(BII)**

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >100 cells/mm^3 for ≥6 months in response to ART **(CII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count decreases to <100 cells/mm^3 **(BIII)**

Treating Acute Infection in Severely Ill Patients

Preferred Therapy:

- Liposomal amphotericin B, 3 to 5 mg/kg/day IV for 2 weeks; followed by itraconazole[a] 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy **(AII)**

Alternative Therapy:

- Voriconazole[a] 6 mg/kg IV q12h for 1 day, then 4 mg/kg q12h for at least 3 days, followed by voriconazole[a] 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy **(BII)**

Treating Mild Disease

Preferred Therapy:

- Itraconazole[a] 200 mg PO BID for 8 weeks **(BII)**, followed by chronic maintenance therapy. **(BII**)

Alternative Therapy:

- Voriconazole[a] 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Itraconazole[a] 200 mg PO daily **(AI)**

Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count >100 cells/mm^3 for ≥6 months in response to ART **(BII)**

Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count <100 cells/mm^3 **(AIII)**, *or*
- If penicilliosis recurs at CD4 count >100 cells/mm^3 **(CIII)**

Other Considerations:

- ART should be administered simultaneously with treatment for penicilliosis to improve outcome. **(CIII)**
- Because of the erratic absorption and potential for drug interactions with ARV therapy, itraconazole concentration should be monitored, and serum concentration should be > 1 mcg/mL.

[a] Both itraconazole and voriconazole can have significant drug-drug interactions with various ARV drugs, dosage adjustment may be necessary, consider therapeutic drug monitoring to guide therapy. See Table 5 for drug interaction information

Key to Acronyms: CD4 = CD4 T lymphocyte; PO = orally; IV = intravenous; q(n)h = every "n" hours; BID = twice daily; ART = antiretroviral therapy, ARV = antriretroviral

References

1. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated Penicillium marneffei infection in southeast Asia. *Lancet*. Jul 9 1994;344(8915):110-113. Available at http://www.ncbi.nlm.nih.gov/pubmed/7912350.
2. Clezy K, Sirisanthana T, Sirisanthana V, Brew B, Cooper DA. Late manifestations of HIV in Asia and the Pacific. *AIDS*. 1994;8 Suppl 2(Suppl 2):S35-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/7857567.
3. Kantipong P, Panich V, Pongsurachet V, Watt G. Hepatic penicilliosis in patients without skin lesions. *Clin Infect Dis*. May 1998;26(5):1215-1217. Available at http://www.ncbi.nlm.nih.gov/pubmed/9597255.
4. Singh PN, Ranjana K, Singh YI, et al. Indigenous disseminated Penicillium marneffei infection in the state of Manipur, India: report of four autochthonous cases. *J Clin Microbiol*. Aug 1999;37(8):2699-2702. Available at http://www.ncbi.nlm.nih.gov/pubmed/10405425.
5. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated Penicillium marneffei infection among HIV-infected patients in Manipur state, India. *J Infect*. Nov 2002;45(4):268-271. Available at http://www.ncbi.nlm.nih.gov/pubmed/12423616.
6. Devi SB, Devi TS, Ningshen R, Devi Kh R, Singh TB, Singh NB. Penicillium morneffei, an emerging AIDS-related pathogen—a RIMS study. *J Indian Med Assoc*. Apr 2009;107(4):208-210. Available at http://www.ncbi.nlm.nih.gov/pubmed/19810362.
7. Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE. Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: regional variation and temporal trends. *Clin Infect Dis*. Mar 15 2001;32(6):955-962. Available at http://www.ncbi.nlm.nih.gov/pubmed/11247718.
8. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clin Infect Dis*. Jan 15 2002;34(2):277-284. Available at http://www.ncbi.nlm.nih.gov/pubmed/11740718.
9. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated Penicillium marneffei infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. Nov 1993;37(11):2407-2411. Available at http://www.ncbi.nlm.nih.gov/pubmed/8285625.
10. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated Penicillium marneffei infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. Jun 1996;173(6):1490-1493. Available at http://www.ncbi.nlm.nih.gov/pubmed/8648227.
11. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated Penicillium marneffei infection in Ho Chi Minh City, Viet Nam. *Clin Infect Dis*. Apr 1 2011;52(7):945-952. Available at http://www.ncbi.nlm.nih.gov/pubmed/21427403.
12. Vanittanakom N, Cooper CR, Jr., Fisher MC, Sirisanthana T. Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. Jan 2006;19(1):95-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/16418525.
13. Supparatpinyo K, Sirisanthana T. Disseminated Penicillium marneffei infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. Feb 1994;18(2):246-247. Available at http://www.ncbi.nlm.nih.gov/pubmed/8161635.
14. Chaiwarith R, Fakthongyoo A, Praparattanapan J, Boonmee D, Sirisanthana T, Supparatpinyo K. Itraconazole vs fluconazole as a primary prophylaxis for fungal infections in HIV-infected patients in Thailand. *Curr HIV Res*. Jul 2011;9(5):334-338. Available at http://www.ncbi.nlm.nih.gov/pubmed/21916838.
15. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated Penicillium marneffei infection in a patient with AIDS. *Clin Infect Dis*. Aug 1994;19(2):357-358. Available at http://www.ncbi.nlm.nih.gov/pubmed/7986922.
16. Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. *AIDS*. Jan 30 2007;21(3):365-367. Available at http://www.ncbi.nlm.nih.gov/pubmed/17255744.
17. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated Penicillium marneffei infection in human immunodeficiency virus-infected patients. *Clin Infect Dis*. May 1998;26(5):1107-1110. Available at http://www.ncbi.nlm.nih.gov/pubmed/9597237.

18. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al. An efficacy study of itraconazole in the treatment of Penicillium marneffei infection. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Dec 1992;75(12):688-691. Available at http://www.ncbi.nlm.nih.gov/pubmed/1339213.

19. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic Penicillium marneffei infections in AIDS patients. *Am J Trop Med Hyg*. Aug 2007;77(2):350-353. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690411.

20. Manosuthi W, Chaovavanich A, Tansuphaswadikul S, et al. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. *J Infect*. Nov 2007;55(5):464-469. Available at http://www.ncbi.nlm.nih.gov/pubmed/17714788.

21. Gupta S, Mathur P, Maskey D, Wig N, Singh S. Immune restoration syndrome with disseminated Penicillium marneffei and cytomegalovirus co-infections in an AIDS patient. *AIDS Res Ther*. 2007;4:21. Available at http://www.ncbi.nlm.nih.gov/pubmed/17922912.

22. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the human immunodeficiency virus. *N Engl J Med*. Dec 10 1998;339(24):1739-1743. Available at http://www.ncbi.nlm.nih.gov/pubmed/9845708.

23. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. Birth defects research. Part A, *Clinical and molecular teratology*. Nov 2005;73(11):919-923. Available at http://www.ncbi.nlm.nih.gov/pubmed/16265639.

Leishmaniasis (Last updated February 6, 2017; last reviewed February 6, 2017)

Epidemiology

Leishmaniasis is caused by protozoa that survive and replicate inside vacuoles within macrophages and other mononuclear cells. The *Leishmania* genus has traditionally been differentiated into multiple species that cause cutaneous, mucosal, and/or visceral disease.[1,2]

Leishmaniasis occurs in 98 countries or territories in the tropics, subtropics, and southern Europe, with an estimated incidence of 1.6 million new cases annually—as many as 1.2 million cases of cutaneous leishmaniasis and 0.4 million cases of visceral leishmaniasis.[3] As of March 2010, HIV-leishmaniasis co-infection has been reported in 35 countries, predominantly as visceral leishmaniasis.[3,4] The first cases of HIV-leishmaniasis co-infection were described in Spain in the late 1980s. During the 1980s and 1990s, more than 90% of co-infection cases were reported in southern Europe.[3,5] After the introduction of combination antiretroviral therapy (ART), the incidence decreased substantially in developed countries,[6,7] but HIV-leishmaniasis co-infection poses a growing problem in parts of Asia, Africa, and Latin America.[3,4,8,9] In one large leishmaniasis specialty hospital in Bihar, India, the prevalence of HIV infection in patients with visceral leishmaniasis has increased from 0.88% in 2000 to 2.18% in 2006.[3] A study in a treatment center in Humera in northwestern Ethiopia reported that 31% of patients with visceral leishmaniasis were co-infected with HIV.[10] Most leishmanial infections in immunocompetent hosts are asymptomatic. In many disease-endemic areas, 30% or more of the population has evidence of latent infection, as demonstrated by a positive leishmanin skin test.[11-13] After primary infection, *Leishmania* remain viable in healthy individuals for long periods, creating a population at risk of reactivation if immunosuppression occurs. In HIV-infected patients without severe immunosuppression, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 T lymphocyte [CD4] cell count <200 cells/mm^3), manifestations of leishmaniasis can be both atypical and more severe. Relapse after treatment—especially of visceral leishmaniasis—is common.[14,15]

In endemic areas, leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*.[2] However, in Southern Europe, HIV and *Leishmania infantum* visceral co-infections were reported in association with injection-drug use, suggesting that *Leishmania* which can be transmitted via blood transfusion, also may be acquired by needle sharing.[16] *Leishmania* parasites were demonstrated in 34% to 52% of used syringes discarded by injection-drug users in Madrid, and, based on molecular characteristics, investigators have described a new, epidemiologically significant leishmaniasis transmission cycle that relies on mechanical transfer of amastigotes via contaminated syringes.[17,18]

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous and visceral leishmaniasis, but also related syndromes, such as mucosal (or mucocutaneous) leishmaniasis, disseminated cutaneous leishmaniasis, diffuse cutaneous leishmaniasis (an anergic form), and post-kala-azar dermal leishmaniasis. The most common clinical presentation of leishmaniasis in HIV-infected individuals is a systemic visceral disease syndrome, but the distribution varies geographically, reflecting differences in the predominant parasite species. In Europe, visceral disease has been reported in 95% of cases (87% typical visceral, 8% atypical visceral).[4,5] In contrast, in Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported cases, respectively.[19]

In patients with HIV and visceral disease, the most common clinical and laboratory findings are fever (65% to 100%), systemic malaise (70% to 90%), splenomegaly (usually moderate) (60% to 90%), hepatomegaly without splenomegaly (34% to 85%), hepatosplenomegaly (68% to 73%), lymphadenopathy (12% to 57%), and pancytopenia (50% to 80%).[5,15] Anemia is usually marked, with <10 g hemoglobin/dL (49% to 100%); leukopenia is moderate, with <2400 leukocytes/μL (56% to 95%); and thrombocytopenia is usually present (52% to 93%). Splenomegaly is less pronounced in HIV-co-infected patients than in immunocompetent

patients with visceral leishmaniasis.[15] In patients with more profound immunosuppression, atypical manifestations have been described, including involvement of the upper and lower gastrointestinal tract, lung, pleural and peritoneal cavities, and skin.[4-6,15,20] Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis.[5] Non-ulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described.[21-23] However, the presence of *Leishmania* amastigotes in skin can occur in the absence of lesions or in combination with other pathology, such as KS, and does not prove that the parasite is the cause of the lesions.[24,25]

Disfiguring mucosal lesions associated with anergy to *Leishmania* antigens have been observed in Europeans with AIDS, in contrast to mucocutaneous disease in immunocompetent patients, which is associated with strong leishmanin skin-test responses.[20,26,27]

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, and smears in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in HIV-co-infected patients.[4,5]

Visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in blood smears (approximately 50% sensitivity in expert hands), buffy-coat smear preparations, cultures from the peripheral blood, and smears or cultures from bone marrow or splenic aspirates. PCR amplification can also be useful for detecting *Leishmania* nucleic acid in the blood or tissue of co-infected patients (>95% sensitivity).[18]

Serologic tests to detect *Leishmania* antbodies are highly sensitivity and can be used to diagnose visceral leishmaniasis in immunocompetent patients.[28] Serology should not be used as a screening test as positive serology can occur in individuals with asymptomatic infection. It should be used only as a confirmatory test in patients with a compatible clinical picture and an exposure history suggestive of visceral leishmaniasis. Serology has a low sensitivity in HIV-infected patients, especially in Europe, such that parasitological diagnosis should be sought when clinical suspicion has been raised.[4,5,29]

The use of recombinant antigen in ELISA assays may increase sensitivity, but a proportion of co-infected patients remain seronegative.[30] Immunoblotting with *Leishmania infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of European patients.[29] Interestingly, reports suggest that the serology sensitivity may remain fairly high in HIV-co-infected patients in Ethiopia (77%-89% in HIV-visceral leishmaniasis co-infected patients, versus 87%–95% in HIV-negative patients).[31] Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV co-infection.[2]

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in areas with zoonotic transmission and vector control activities, such as indoor residual spraying and/or use of insecticide-treated bed nets. The best way for travelers to leishmaniasis-endemic areas to prevent infection is to protect themselves from sand fly bites. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin.

Measures to decrease transmission of infectious agents, including *Leishmania* parasites, in injection-drug users, such as the use of clean needles and injection works from syringe (needle) exchange programs, are appropriate.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended, and no screening or preemptive therapy is appropriate for HIV-infected patients who may have been exposed to leishmanial infection. No

vaccine against leishmaniasis is available.

Treating Disease

Visceral Leishmaniasis

For HIV-infected patients with visceral leishmaniasis, conventional and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.[4,32-35] Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than conventional amphotericin B (amphotericin B deoxycholate) or pentavalent antimony (sodium stibogluconate).[36-38] The equivalent efficacy and better toxicity profile have led most clinicians to regard liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-co-infected patients **(AII)**.[4,39] The optimal amphotericin B dosage has not been determined.[39,40] Regimens with efficacy include liposomal preparations of 2 to 4 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight **(AII)**, or amphotericin B deoxycholate, 0.5 to 1.0 mg/kg body weight/day intravenously (IV), to achieve a total dose of 1.5 to 2.0 g **(BII)**.[32,35,39,41-43] Pentavalent antimony (sodium stibogluconate), which is available in the United States through the Centers for Disease Control and Prevention (CDC), 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, may be considered as an alternative **(BII)**.

Additional treatment options for visceral leishmaniasis in HIV-co-infected patients, which are recommended primarily because of their use in non-HIV-infected patients. include oral miltefosine, which is available in the United States via www.Profounda.com, and the parenteral formulation of the aminoglycoside paromomycin, which is not available in the United States.[40,44] In general, the target dose of miltefosine is ~2.5 mg/kg daily (maximum of 150 mg daily), and the initial treatment course is 28 days. Gastrointestinal symptoms are common but typically do not limit treatment. Data supporting the use of miltefosine in HIV-co-infected patients are relatively limited **(CIII)**.[45,46] Parenteral paromomycin has been used successfully to treat visceral leishmaniasis in HIV-negative patients, particularly in India.[40] Essentially no efficacy data are available for paromomycin in HIV-co-infected patients. A clinical trial of combination therapy (liposomal amphotericin B plus miltefosine or paromomycin; miltefosine plus paromomycin) produced promising results in non-HIV-infected patients in India whose visceral leishmaniasis was not severe.[47] Further research is needed to validate the efficacy of drug combinations, including for severe or refractory cases of visceral leishmaniasis in various geographic regions and in HIV-co-infected patients.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous, mucocutaneous, or diffuse cutaneous leishmaniasis in HIV-co-infected patients. On the basis of data in HIV-negative patients with cutaneous leishmaniasis and case reports in HIV-co-infected patients, HIV-infected patients should be treated with liposomal amphotericin B **(BIII)** as previously outlined,[48] or pentavalent antimony (sodium stibogluconate), depending on the form of the disease and the clinical response **(BIII)**.[2,49,50] However, pentavalent antimony can increase viral transcription and HIV replication in cultures of human peripheral blood mononuclear cells, raising concerns about its use in HIV-infected patients.[51]

Potential alternatives for cutaneous leishmaniasis include miltefosine, topical paromomycin, intralesional pentavalent antimony, and local heat therapy. However, no data exist for co-infected patients, and in immunocompetent patients, the effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.[40,52-54]

Special Considerations with Regard to Starting ART

ART should be initiated or optimized following standard practice for HIV-infected patients **(AIII)**. There are no leishmaniasis-specific data on when to start ART. Appropriate use of ART has substantially improved the survival of co-infected patients in Europe and decreased the likelihood of relapse after antileishmanial

therapy.[7,15,55] Therefore, ART should be started as soon as patients are able to tolerate it **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients treated with liposomal amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions **(AII)**. Infusional adverse events are ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids **(BII)**. Infusion of 1 L of saline one hour prior to drug infusion can help reduce the risk of glomerular function decline during treatment **(BIII)**. The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for amphotericin B deoxycholate.[37] Amphotericin B deoxycholate treatment is also associated with an increased risk of anemia.[33]

Patients receiving pentavalent antimony (sodium stibogluconate) should be monitored closely for adverse reactions.[49] Overall, at a dose of 20 mg/kg of body weight per day, greater than 60% of patients have 1 or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and (in some patients) clinical pancreatitis. Weekly electrocardiograms are recommended during treatment, with careful monitoring for changes that may indicate early cardiotoxicity, such as prolonged QT intervals and T-wave inversion **(CIII)**. Rarely, arrhythmias and sudden death have occurred.[33,41] Severe adverse reactions to pentavalent antimony (sodium stibogluconate), including acute pancreatitis and leukopenia, appear to be more common in co-infected patients than in those who are not infected with HIV.[56]

Cases of newly symptomatic visceral and cutaneous leishmaniasis have been reported in association with immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.[57,58] Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.[59-62] Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

Managing Treatment Failure

For patients who fail to respond to initial therapy or who experience a relapse after initial treatment, a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy, should be used as previously outlined **(AIII)**. The response rate for retreatment appears to be similar to that for initial therapy, although some patients evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.

Immunotherapy, including interferon-gamma and recombinant human granulocyte macrophage colony stimulating factor (GM-CSF), has been used experimentally as an adjunct to antileishmanial treatment for refractory cases.[63,64] However, a clinical trial of pentavalent antimony (sodium stibogluconate) plus interferon-gamma for visceral leishmaniasis in HIV-co-infected patients was suspended when an interim analysis indicated that there was no advantage over pentavalent antimony (sodium stibogluconate) alone.[41] In addition, the use of interferon-gamma was reported to be associated with acceleration of KS in two patients with visceral leishmaniasis and HIV co-infection.[24]

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of antileishmanial therapy in HIV-infected patients, and frequency of relapse is inversely related to CD4 cell count. In HIV-co-infected patients with visceral leishmaniasis who were not receiving or responding to ART, the risk of relapse at 6 and 12 months was 60% and 90%, respectively, in the absence of secondary prophylaxis (chronic maintenance therapy).[5,65] Therefore, secondary prophylaxis with an effective antileishmanial drug, administered at least every 2 to 4 weeks, is recommended, particularly for patients with visceral leishmaniasis and CD4 cell counts <200 cells/μL **(AII)**.[5,15,34,65]

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex

(3 mg/kg every 21 days) in 8 patients to no prophylaxis in 9 patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.[34] In retrospective observational studies, monthly pentavalent antimony (sodium stibogluconate) or lipid formulations of amphotericin every 2 to 4 weeks were also associated with decreased relapse rates.[15,65] Liposomal amphotericin B (4 mg/kg every 2–4 weeks) or amphotericin B lipid complex (3 mg/kg every 21 days) should be used for secondary prophylaxis **(AII)**. Pentavalent antimony (sodium stibogluconate), 20 mg/kg IV or IM every 4 weeks, is an alternative **(BII)**. Although pentamidine is no longer recommended to treat primary visceral leishmaniasis, a dosage of 6 mg/kg IV every 2 to 4 weeks has been suggested as another alternative for secondary prophylaxis **(CIII)**.[66] Allopurinol, used for maintenance therapy in a dose of 300 mg orally 3 times daily, is less effective than monthly pentavalent antimony and **is not recommended (BII)**.[65] Although no published data on efficacy are available, maintenance therapy may be indicated for immunocompromised patients with cutaneous leishmaniasis who have multiple relapses after adequate treatment **(CIII)**.

When to Stop Secondary Prophylaxis

Some investigators suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm^3 in response to ART.[67] Others, however, suggest that secondary prophylaxis should be maintained indefinitely. In one study, a positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse.[68] Thus, because there is a paucity of published data or clinical trial experience, no recommendation can be made regarding discontinuation of secondary prophylaxis in HIV-*Leishmania*-co-infected persons.

Special Considerations During Pregnancy

Diagnostic considerations are the same in pregnant women as in women who are not pregnant. One study suggests that lesions of cutaneous leishmaniasis may be larger and are more likely to be exophytic in pregnancy, and that untreated cutaneous leishmaniasis may be associated with an increased risk of preterm delivery and stillbirth.[69] Labels for pentavalent antimony compounds (sodium stibogluconate, available in the United States through CDC, and meglumine antimoniate) state that these drugs are contraindicated for use in pregnant women, although various antimonial compounds were not teratogenic in chickens, rats, or sheep.[70-72] Good clinical and pregnancy outcomes have been reported for small series of pregnant women treated with meglumine antimoniate, amphotericin B deoxycholate, or liposomal amphotericin B.[73-76] Retrospective analyses suggest that rates of preterm birth and spontaneous abortion may be increased in women with visceral leishmaniasis during pregnancy, especially in the first trimester and when antimonial drugs are used.[77,78] Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy **(AIII)**.[74] The alternatives are amphotericin B deoxycholate **(AIII)** or pentavalent antimony (sodium stibogluconate) **(AIII)**. No data are available on the use of parenteral paromomycin in pregnancy, but concerns have been raised about fetal ototoxicity with other aminoglycosides used in pregnancy. Miltefosine is teratogenic and is contraindicated in pregnancy.[40] Perinatal transmission of *Leishmania spp.* is rare; 13 documented cases have been reported.[77,79-81] No data are available on the risk of transmission of *Leishmania spp.* in HIV-infected pregnant women.

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 mg/kg IV daily **(AII)**, *or*
- Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) **(AII)**
- Achieve a total dose of 20–60 mg/kg **(AII)**

Alternative Therapy:

- Other amphotericin B lipid complex dosed as above, *or*
- Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams **(BII)**, *or*
- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days **(BII)**. (Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100.)
- Miltefosine **(CIII)** (available in the United States via www.Profounda.com)
- For patients who weigh 30–44 kg: 50 mg PO bid for 28 days
- For patients who weigh ≥45 kg: 50 mg PO tid for 28 days

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication:

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm^3 **(AII)**

Preferred Therapy:

- Liposomal amphotericin B 4 mg/kg every 2–4 weeks **(AII)**, *or*
- Amphotericin B Lipid Complex 3 mg/kg every 21 days **(AII)**

Alternative Therapy:

- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM every 4 weeks **(BII)**

Discontinuation of Chronic Maintenance Therapy

Some investigators suggest that therapy can be discontinued after a sustained (>3 to 6 months) increase in CD4 count to >200 to 350 cells/mm^3 in response to ART, but others suggest that therapy should be continued indefinitely. Therefore, no recommendation can be made regarding discontinuation of chronic maintenance therapy.

Treating Cutaneous Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII)**, *or*
- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days **(BIII)**

Alternative Therapy:

- Other options include oral miltefosine (can be obtained in the United States through a treatment IND), topical paromomycin, intralesional pentavalent antimony (sodium stibogluconate), or local heat therapy.

Chronic Maintenance Therapy for Cutaneous Leishmaniasis

- May be indicated for immunocompromised patients with multiple relapses **(CIII)**

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CDC = Centers for Disease Control and Prevention; IM = intramuscular; IND = investigational new drug; IV = intravenous

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis*. Sep 2004;27(5):305-318. Available at http://www.ncbi.nlm.nih.gov/pubmed/15225981.
2. Jeronimo SMB, de Queiroz Sousa A, Pearson RD. Leishmaniasis. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical infectious diseases: principles, pathogens and practice*. Edinburgh, Scotland: Churchill Livingstone Elsevier; 2006:1095-1113.
3. World Health Organization. Leishmaniasis. Available at http://www.who.int/leishmaniasis/burden/en/. Accessed March

21, 2013.

4. Murray HW. Leishmaniasis in the United States: treatment in 2012. *Am J Trop Med Hyg*. Mar 2012;86(3):434-440. Available at http://www.ncbi.nlm.nih.gov/pubmed/22403313.
5. Alvar J, Canavate C, Gutierrez-Solar B, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev*. Apr 1997;10(2):298-319. Available at http://www.ncbi.nlm.nih.gov/pubmed/9105756.
6. Rosenthal E, Marty P, del Giudice P, et al. HIV and Leishmania coinfection: a review of 91 cases with focus on atypical locations of Leishmania. *Clin Infect Dis*. Oct 2000;31(4):1093-1095. Available at http://www.ncbi.nlm.nih.gov/pubmed/11049794.
7. Tortajada C, Perez-Cuevas B, Moreno A, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. *J Acquir Immune Defic Syndr*. Jul 1 2002;30(3):364-366. Available at http://www.ncbi.nlm.nih.gov/pubmed/12131576.
8. Mathur P, Samantaray JC, Vajpayee M, Samanta P. Visceral leishmaniasis/human immunodeficiency virus co-infection in India: the focus of two epidemics. *J Med Microbiol*. Jul 2006;55(Pt 7):919-922. Available at http://www.ncbi.nlm.nih.gov/pubmed/16772420.
9. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging Leishmania/HIV co-infection in Africa. *Med Microbiol Immunol*. Nov 2001;190(1-2):65-67. Available at http://www.ncbi.nlm.nih.gov/pubmed/11770113.
10. ter Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. *Clin Infect Dis*. Jun 1 2008;46(11):1702-1709. Available at http://www.ncbi.nlm.nih.gov/pubmed/18419422.
11. Marty P, Le Fichoux Y, Giordana D, Brugnetti A. Leishmanin reaction in the human population of a highly endemic focus of canine leishmaniasis in Alpes-Maritimes, France. *Trans R Soc Trop Med Hyg*. May-Jun 1992;86(3):249-250. Available at http://www.ncbi.nlm.nih.gov/pubmed/1412644.
12. Moral L, Rubio EM, Moya M. A leishmanin skin test survey in the human population of l'Alacanti region (Spain): implications for the epidemiology of Leishmania infantum infection in southern Europe. *Trans R Soc Trop Med Hyg*. Mar-Apr 2002;96(2):129-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/12055798.
13. Werneck GL, Rodrigues L, Santos MV, et al. The burden of Leishmania chagasi infection during an urban outbreak of visceral leishmaniasis in Brazil. *Acta Trop*. Jul 2002;83(1):13-18. Available at http://www.ncbi.nlm.nih.gov/pubmed/12062788.
14. Lopez-Velez R, Perez-Molina JA, Guerrero A, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and Leishmania in an area of Madrid, Spain. *Am J Trop Med Hyg*. Apr 1998;58(4):436-443. Available at http://www.ncbi.nlm.nih.gov/pubmed/9574788.
15. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. *Medicine (Baltimore)*. Jan 2001;80(1):54-73. Available at http://www.ncbi.nlm.nih.gov/pubmed/11204503.
16. Alvar J, Jimenez M. Could infected drug-users be potential Leishmania infantum reservoirs? *AIDS*. Jun 1994;8(6):854. Available at http://www.ncbi.nlm.nih.gov/pubmed/8086149.
17. Chicharro C, Morales MA, Serra T, Ares M, Salas A, Alvar J. Molecular epidemiology of Leishmania infantum on the island of Majorca: a comparison of phenotypic and genotypic tools. *Trans R Soc Trop Med Hyg*. Apr 2002;96 Suppl 1:S93-99. Available at http://www.ncbi.nlm.nih.gov/pubmed/12055859.
18. Cruz I, Morales MA, Noguer I, Rodriguez A, Alvar J. Leishmania in discarded syringes from intravenous drug users. *Lancet*. Mar 30 2002;359(9312):1124-1125. Available at http://www.ncbi.nlm.nih.gov/pubmed/11943264.
19. Rabello A, Orsini M, Disch J. Leishmania/HIV co-infection in Brazil: an appraisal. *Ann Trop Med Parasitol*. Oct 2003;97 Suppl 1:17-28. Available at http://www.ncbi.nlm.nih.gov/pubmed/14678630.
20. Mota Sasaki M, Matsumo Carvalho M, Schmitz Ferreira ML, Machado MP. Cutaneous Leishmaniasis Coinfection in AIDS Patients: Case Report and Literature Review. *Braz J Infect Dis*. Jun 1997;1(3):142-144. Available at http://www.ncbi.nlm.nih.gov/pubmed/11105130.
21. Gonzalez-Beato MJ, Moyano B, Sanchez C, et al. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. *Br J Dermatol*. Dec 2000;143(6):1316-1318. Available at http://www.ncbi.nlm.nih.gov/pubmed/11122042.

22. Carnauba D, Jr., Konishi CT, Petri V, Martinez IC, Shimizu L, Pereira-Chioccola VL. Atypical disseminated leishmaniasis similar to post-kala-azar dermal leishmaniasis in a Brazilian AIDS patient infected with Leishmania (Leishmania) infantum chagasi: a case report. *Int J Infect Dis*. Nov 2009;13(6):e504-507. Available at http://www.ncbi.nlm.nih.gov/pubmed/19447660.

23. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. *Br J Dermatol*. Feb 2009;160(2):311-318. Available at http://www.ncbi.nlm.nih.gov/pubmed/19187345.

24. Albrecht H, Stellbrink HJ, Gross G, Berg B, Helmchen U, Mensing H. Treatment of atypical leishmaniasis with interferon gamma resulting in progression of Kaposi's sarcoma in an AIDS patient. *Clin Investig*. Dec 1994;72(12):1041-1047. Available at http://www.ncbi.nlm.nih.gov/pubmed/7711412.

25. Bosch RJ, Rodrigo AB, Sanchez P, de Galvez MV, Herrera E. Presence of Leishmania organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral leishmaniasis. *Int J Dermatol*. Oct 2002;41(10):670-675. Available at http://www.ncbi.nlm.nih.gov/pubmed/12390190.

26. Canovas DL, Carbonell J, Torres J, Altes J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. *J Laryngol Otol*. Dec 1994;108(12):1089-1092. Available at http://www.ncbi.nlm.nih.gov/pubmed/7861090.

27. Miralles ES, Nunez M, Hilara Y, Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. *Dermatology*. 1994;189(3):275-277. Available at http://www.ncbi.nlm.nih.gov/pubmed/7949483.

28. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol*. Sep 2002;9(5):951-958. Available at http://www.ncbi.nlm.nih.gov/pubmed/12204943.

29. Medrano FJ, Canavate C, Leal M, Rey C, Lissen E, Alvar J. The role of serology in the diagnosis and prognosis of visceral leishmaniasis in patients coinfected with human immunodeficiency virus type-1. *Am J Trop Med Hyg*. Jul 1998;59(1):155-162. Available at http://www.ncbi.nlm.nih.gov/pubmed/9684645.

30. Houghton RL, Petrescu M, Benson DR, et al. A cloned antigen (recombinant K39) of Leishmania chagasi diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. *J Infect Dis*. May 1998;177(5):1339-1344. Available at http://www.ncbi.nlm.nih.gov/pubmed/9593022.

31. ter Horst R, Tefera T, Assefa G, Ebrahim AZ, Davidson RN, Ritmeijer K. Field evaluation of rK39 test and direct agglutination test for diagnosis of visceral leishmaniasis in a population with high prevalence of human immunodeficiency virus in Ethiopia. *Am J Trop Med Hyg*. Jun 2009;80(6):929-934. Available at http://www.ncbi.nlm.nih.gov/pubmed/19478251.

32. Davidson RN, Di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med*. Feb 1994;87(2):75-81. Available at http://www.ncbi.nlm.nih.gov/pubmed/8153291.

33. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS*. Jun 18 1999;13(9):1063-1069. Available at http://www.ncbi.nlm.nih.gov/pubmed/10397536.

34. Lopez-Velez R, Videla S, Marquez M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother*. Mar 2004;53(3):540-543. Available at http://www.ncbi.nlm.nih.gov/pubmed/14739148.

35. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect*. Mar 1996;32(2):133-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/8708370.

36. Lazanas MC, Tsekes GA, Papandreou S, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. *AIDS*. Jul 1993;7(7):1018-1019. Available at http://www.ncbi.nlm.nih.gov/pubmed/8357549.

37. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis*. Feb 1 2004;38(3):377-383. Available at http://www.ncbi.nlm.nih.gov/pubmed/14727208.

38. Torre-Cisneros J, Villanueva JL, Kindelan JM, Jurado R, Sanchez-Guijo P. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. *Clin*

Infect Dis. Oct 1993;17(4):625-627. Available at http://www.ncbi.nlm.nih.gov/pubmed/8268341.

39. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis*. Oct 1 2006;43(7):917-924. Available at http://www.ncbi.nlm.nih.gov/pubmed/16941377.
40. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol*. 2006;61:223-274. Available at http://www.ncbi.nlm.nih.gov/pubmed/16735166.
41. Laguna F, Videla S, Jimenez-Mejias ME, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. *J Antimicrob Chemother*. Sep 2003;52(3):464-468. Available at http://www.ncbi.nlm.nih.gov/pubmed/12888588.
42. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis*. Jan 1999;28(1):42-48; discussion 49-51. Available at http://www.ncbi.nlm.nih.gov/pubmed/10028069.
43. Laguna F, Torre-Cisneros J, Moreno V, Villanueva JL, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. Sep 1995;21(3):711-712. Available at http://www.ncbi.nlm.nih.gov/pubmed/8527591.
44. Sundar S, T. K. Jha CPT, S. K. Bhattacharya and M. Rai. Oral miltefosine for the treatment of Indian visceral leishmaniasis. *Trans R Soc Trop Med Hyg*. 2006. Available at http://ncbi.nlm.nih.gov/pubmed/16730038.
45. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis*. Aug 1 2006;43(3):357-364. Available at http://www.ncbi.nlm.nih.gov/pubmed/16804852.
46. Sindermann H, K. R. Engel CFaWB. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis*. 39(10): 1520-3. 2004. Available at http://www.ncbi.nlm.nih.gov/pubmed/15546090.
47. Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet*. Feb 5 2011;377(9764):477-486. Available at http://www.ncbi.nlm.nih.gov/pubmed/21255828.
48. Wortmann G, Zapor M, Ressner R, et al. Lipsosomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg*. Nov 2010;83(5):1028-1033. Available at http://www.ncbi.nlm.nih.gov/pubmed/21036832.
49. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg*. Mar 1992;46(3):296-306. Available at http://www.ncbi.nlm.nih.gov/pubmed/1313656.
50. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis*. Sep 2007;7(9):581-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/17714672.
51. Barat C, Zhao C, Ouellette M, Tremblay MJ. HIV-1 replication is stimulated by sodium stibogluconate, the therapeutic mainstay in the treatment of leishmaniasis. *J Infect Dis*. Jan 15 2007;195(2):236-245. Available at http://www.ncbi.nlm.nih.gov/pubmed/17191169.
52. Belay AD, Asafa Y, Mesure J, Davidson RN. Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy. *Ann Trop Med Parasitol*. Apr 2006;100(3):223-227. Available at http://www.ncbi.nlm.nih.gov/pubmed/16630379.
53. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by Leishmania tropica in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis*. Apr 15 2005;40(8):1148-1155. Available at http://www.ncbi.nlm.nih.gov/pubmed/15791515.
54. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis*. May 1 2004;38(9):1266-1272. Available at http://www.ncbi.nlm.nih.gov/pubmed/15127339.
55. de la Rosa R, Pineda JA, Delgado J, et al. Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. Feb 15 2001;32(4):633-635. Available at http://www.ncbi.nlm.nih.gov/pubmed/11181128.
56. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am J Trop Med Hyg*. Nov 1999;61(5):766-769. Available at http://www.ncbi.nlm.nih.gov/pubmed/10586909.

57. Berry A, Abraham B, Dereure J, Pinzani V, Bastien P, Reynes J. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. *Scand J Infect Dis*. 2004;36(3):225-227. Available at http://www.ncbi.nlm.nih.gov/pubmed/15119371.

58. Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. *J Infect Dis*. Nov 15 2005;192(10):1819-1822. Available at http://www.ncbi.nlm.nih.gov/pubmed/16235183.

59. Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, et al. Tegumentary leishmaniasis as the cause of immune reconstitution inflammatory syndrome in a patient co-infected with human immunodeficiency virus and Leishmania guyanensis. *Am J Trop Med Hyg*. Oct 2009;81(4):559-564. Available at http://www.ncbi.nlm.nih.gov/pubmed/19815866.

60. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *Int J Dermatol*. Dec 2008;47(12):1263-1270. Available at http://www.ncbi.nlm.nih.gov/pubmed/19126013.

61. Tadesse A, Hurissa Z. Leishmaniasis (PKDL) as a case of immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patient after initiation of anti-retroviral therapy (ART). *Ethiop Med J*. Jan 2009;47(1):77-79. Available at http://www.ncbi.nlm.nih.gov/pubmed/19743785.

62. Antinori S, Longhi E, Bestetti G, et al. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. *Br J Dermatol*. Nov 2007;157(5):1032-1036. Available at http://www.ncbi.nlm.nih.gov/pubmed/17854365.

63. Badaro R, Johnson WD, Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. *J Infect Dis*. Mar 1993;167 Suppl 1(Suppl 1):S13-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/8433014.

64. Badaro R, Nascimento C, Carvalho JS, et al. Granulocyte-macrophage colony-stimulating factor in combination with pentavalent antimony for the treatment of visceral Leishmaniasis. *Eur J Clin Microbiol Infect Dis*. 1994;13 Suppl 2:S23-28. Available at http://www.ncbi.nlm.nih.gov/pubmed/7875148.

65. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. *Am J Med*. May 1996;100(5):496-501. Available at http://www.ncbi.nlm.nih.gov/pubmed/8644760.

66. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Trop Med Int Health*. Sep 2009;14(9):1064-1070. Available at http://www.ncbi.nlm.nih.gov/pubmed/19552658.

67. Berenguer J, Cosin J, Miralles P, Lopez JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. *AIDS*. Dec 22 2000;14(18):2946-2948. Available at http://www.ncbi.nlm.nih.gov/pubmed/11153679.

68. Bourgeois N, Bastien P, Reynes J, Makinson A, Rouanet I, Lachaud L. 'Active chronic visceral leishmaniasis' in HIV-1-infected patients demonstrated by biological and clinical long-term follow-up of 10 patients. *HIV Med*. Nov 2010;11(10):670-673. Available at http://www.ncbi.nlm.nih.gov/pubmed/20500233.

69. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis*. Aug 15 2007;45(4):478-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/17638198.

70. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. *Am J Vet Res*. Jan 1966;27(116):132-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/5913019.

71. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. *Ann N Y Acad Sci*. Aug 8 1952;55(2):203-215. Available at http://www.ncbi.nlm.nih.gov/pubmed/12977037.

72. Rossi F, Acampora R, Vacca C, et al. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. *Teratog Carcinog Mutagen*. 1987;7(5):491-496. Available at http://www.ncbi.nlm.nih.gov/pubmed/2893463.

73. Gradoni L, Gaeta GB, Pellizzer G, Maisto A, Scalone A. Mediterranean visceral leishmaniasis in pregnancy. *Scand J*

Infect Dis. 1994;26(5):627-629. Available at http://www.ncbi.nlm.nih.gov/pubmed/7855563.

74. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother*. Feb 2005;55(2):229-233. Available at http://www.ncbi.nlm.nih.gov/pubmed/15649998.
75. Topno RK, Pandey K, Das VN, et al. Visceral leishmaniasis in pregnancy - the role of amphotericin B. *Ann Trop Med Parasitol*. Apr 2008;102(3):267-270. Available at http://www.ncbi.nlm.nih.gov/pubmed/18348781.
76. Utili R, Rambaldi A, Tripodi MF, Andreana A. Visceral leishmaniasis during pregnancy treated with meglumine antimoniate. *Infection*. May-Jun 1995;23(3):182-183. Available at http://www.ncbi.nlm.nih.gov/pubmed/7499009.
77. Adam GK, Abdulla MA, Ahmed AA, Adam I. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. *Int J Gynaecol Obstet*. Dec 2009;107(3):208-210. Available at http://www.ncbi.nlm.nih.gov/pubmed/19766208.
78. Mueller M, Balasegaram M, Koummuki Y, Ritmeijer K, Santana MR, Davidson R. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother*. Oct 2006;58(4):811-815. Available at http://www.ncbi.nlm.nih.gov/pubmed/16916865.
79. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Loscher T. Congenital visceral leishmaniasis. *Emerg Infect Dis*. Feb 2006;12(2):359-360. Available at http://www.ncbi.nlm.nih.gov/pubmed/17080586.
80. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics*. Nov 1999;104(5):e65. Available at http://www.ncbi.nlm.nih.gov/pubmed/10545591.
81. Zinchuk A, Nadraga A. Congenital visceral leishmaniasis in Ukraine: case report. *Ann Trop Paediatr*. 2010;30(2):161-164. Available at http://www.ncbi.nlm.nih.gov/pubmed/20522305.

Chagas Disease (Last updated September 24, 2015; last reviewed September 24, 2015)

Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*, and transmitted to humans by infected triatomine bugs, and less commonly by transfusion, organ transplant, from mother to infant, and in rare instances, by ingestion of contaminated food or drink.[1-4] The hematophagous triatomine vectors defecate during or immediately after feeding on a person. The parasite is present in large numbers in the feces of infected bugs, and enters the human body through the bite wound, or through the intact conjunctiva or other mucous membrane.

Vector-borne transmission occurs only in the Americas, where an estimated 8 to 10 million people have Chagas disease.[5] Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.[4] In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America, and large-scale migration has brought infected individuals to cities both within and outside of Latin America.[4,6,7]

Infected triatomine vectors and *T. cruzi*-infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.[8-10] However, the risk of vector-borne infection within the United States appears to be very low, probably because of better housing conditions and less efficient vectors.[11] *T. cruzi* also can be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.[12,13] Currently an estimated 90% of the U.S. blood supply is screened.

For these reasons, the vast majority of the estimated 300,000 individuals in the United States with Chagas disease are thought to be immigrants who acquired the infection while living in endemic areas in Latin America.[14] In patients chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV disease) may lead to reactivation disease characterized by parasitemia, associated with increased intracellular parasite replication and lack of immunological control of the infection.[15-17]

Clinical Manifestations

The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.[2,4] If the portal of infection was the conjunctiva, patients may develop the characteristic Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective etiologic treatment, *T. cruzi* infection passes into the chronic phase.[2,18]

Most patients with chronic *T. cruzi* infection have no signs or symptoms, and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of them will progress to clinically evident Chagas disease, most commonly cardiomyopathy.[2,18] The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.[4,19] Over time, the disease may progress to higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, congestive heart failure, ventricular aneurysm, and complete heart block are poor prognostic signs, associated with high rates of short-term mortality, including sudden death.[20] Chagas digestive disease is much less common than cardiomyopathy, and seen predominantly in infected patients in parts of Brazil and Bolivia.[21] Dysphagia is

the characteristic symptom of megaesophagus, and prolonged constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, usually detectable by microscopy, and can occur in the settings of immunosuppressive therapy to prevent transplant rejection and cancer chemotherapy, as well as in HIV-infected patients.[16,22-26] Even in the absence of symptoms, patients with chronic Chagas disease who are HIV-co-infected have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.[25] Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts <200 cells/mm^3, a history of prior opportunistic infections, or both.[16]

The clinical features of reactivated Chagas disease in patients with HIV infection differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).[15,16,27,28] The presentation may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of AIDS patients with CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in HIV-infected patients is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.[16,17] Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation or rapid progression of existing chronic cardiomyopathy.[16,29] Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach or intestine.[16,29]

Diagnosis

Most patients infected with Chagas disease, including those in the United States, are in the chronic phase and typically unaware of their infection. Screening for infection in patients with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for HIV-infected patients because of the risk of reactivation disease. Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) are used in parallel to improve the accuracy. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.[30,31] Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.[32,33] Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.[30,34] In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection. The sensitivity is highly variable and depends on patient characteristics as well as PCR primers and methods.[35,36]

In HIV-infected patients with epidemiologic risk factors for Chagas disease, co-infection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.[16,26,27] The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than Toxoplasma lesions.[17,27,28] Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells, and less often, in neurons. Cerebrospinal fluid (CSF) shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.[16,17,27,28] In a case series that included 15 HIV and *T. cruzi*-co-infected patients with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.[15,16,27,28]

A definitive diagnosis of re-activation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF or in blood.[16] Circulating parasites are rarely detected microscopically in immunocompetent patients with chronic Chagas disease or in HIV-co-infected patients in the absence of reactivation.[25] If observed in an HIV-*T. cruzi*-co-infected patient, circulating parasites suggest reactivation and the need for treatment. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.[37] In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Centrifugation and microscopic examination of CSF also can be employed for patients with suspected CNS Chagas disease. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods, but takes 2 to 8 weeks to demonstrate parasites.

Conventional PCR is not useful for diagnosing re-activation, because the method can yield a positive result in chronic *T. cruzi* infection in the absence of re-activation.[35,36] However, quantitative PCR assays (real-time PCR) performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.[38,39] Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.[40]

Preventing Exposure

Travelers to endemic countries may be at risk for infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings constructed of adobe brick, mud, or thatch.[41] Because the insects feed at night, individuals who live in or visit Chagas disease-endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.[42]

Most blood products in the United States are screened routinely for *T. cruzi* but screening is not universal in the United States or in others areas, including parts of Latin America.[43]

Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

Clinical manifestations of Chagas disease in HIV-positive patients usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected patients with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.[18] A single course of treatment with benznidazole or nifurtimox can be considered for *T. cruzi*-infected individuals who have not been previously treated and who do not have advanced Chagas cardiomyopathy **(CIII)**. However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.[31,44] Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in co-infected patients **(BIII)**. Most symptomatic reactivation cases have occurred in patients who were not taking ART.[16]

Treating Disease

Chemotherapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute, early-chronic, and re-activated disease.[44,45] These drugs have limited efficacy, however, in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole (5 to 8 mg/kg/day for 30 to 60 days) is the initial treatment most commonly recommended **(BIII)**. Nifurtimox (8 to 10 mg/kg/day, administered for 90 to 120 days) is an alternative **(CIII)**. The duration of therapy with either of these agents has not been studied in patients co-infected with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection, even in patients who receive chemotherapy.[16,27] Limited data suggest that early recognition and treatment of

reactivation may improve prognosis.[16]

Neither anti-trypanosomal drug is licensed in the United States; however, the drugs are available from the Centers for Disease Control and Prevention (CDC) Drug Service for use under investigational protocols. Consultations and drug requests should be addressed to Division of Parasitic Diseases and Malaria Public Inquiries line (770-488-7775; parasites@cdc.gov), the CDC Drug Service (404-718-4745), and for emergencies after business hours, on weekends, and federal holidays through the CDC Emergency Operations Center (770-488-7100).

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasite infections that localize in the CNS, the decision to initiate antiretroviral therapy (ART) must be carefully considered in HIV-infected patients with reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease as soon as their CNS disease is clinically stable **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.[46] Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

As stated above, no reports are available regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients with *T. cruzi* reactivation who fail to respond or who relapse after initial antitrypanosomal therapy **(AIII)**. A publication documents a single case of a *T. cruzi*-infected patient on immunosuppressive therapy for systemic lupus erythematosus who had a good response to posaconazole after failure of benznidazole treatment; failure of benznidazole and response to posaconazole were documented by real-time PCR assays in serial specimens.[47] However, the results of a randomized clinical trial comparing the efficacy and safety of low and high dose posaconazole to that of benznidazole demonstrated that posaconazole was not efficacious for treatment of chronic Chagas disease.[48]

Preventing Recurrence

Patients with HIV infection are at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection.[16] The drugs are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.[44] Because the drugs are toxic and experience with their use in HIV-infected patients is limited, expert advice should be sought.[45] Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when potent ART is used.

Special Considerations During Pregnancy

As recommended for all individuals with epidemiological risk of Chagas disease, screening of pregnant women who have lived in endemic areas should be considered to identify maternal infection and possible risk of infection in their offspring. In pregnant women in areas where the disease is endemic in Latin America, the seroprevalence of *T. cruzi* infection can be as high as 30%.[14,49] In the United States, a 1999 study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of non-Hispanic women and a 2013 study of 4,000 predominantly Hispanic women in the same city found 0.25% with confirmed infection.[50,51]

From 1% to 10% of infants of *T. cruzi*-infected mothers are born with acute *T. cruzi* infection.[14,49] Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases. Studies from the 1980s suggest that congenital transmission of *T. cruzi* may increase the risk of spontaneous abortion, stillbirth, and low birthweight.[52] In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningo-encephalitis, and/or respiratory insufficiency, with high risk of mortality.[49] Limited data suggest that the rate of congenital transmission is higher for HIV-infected women than in immunocompetent mothers.[16,53] Infants co-infected with HIV and *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.[54,55]

Minimal data are available on potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.[56,57] Benznidazole crosses the placenta in rats and covalently binds to fetal proteins.[58] Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection in pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy. For HIV-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, ART should be initiated **(AIII)** as initial treatment. Two cases of treatment of Chagas disease in pregnancy with benzdidazole have been reported. One report was of an acute infection with treatment continued for the first few weeks of an subsequently diagnosed pregnancy, with normal infant outcome,[59] and one was of treatment of an HIV-infected woman with severe immunosuppression with Chagasic encephalitis in the third trimester of pregnancy.[60] The infant was small for gestational age but otherwise healthy and without evidence of *T. cruzi* infection. All infants born to *T. cruzi*-infected women should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.[14,61]

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Clinical Disease

Indication

- Individuals with epidemic risk factors for Chagas disease and tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy.
  - A single course of benznidazole or nifurtimox can be considered (doses and duration same as for treatment of disease) **(CIII)**. However, the efficacy of this therapy is suboptimal, and treated patients are still at risk of reactivation.
  - Initiation or optimization of ART may prevent reactivation of Chagas disease **(BIII)**

Treating Chagas Disease

Note: Treatment is effective in reducing parasitemia and preventing clinical manifestation or slowing progression in patients with acute, early-chronic, and re-activated disease. They have limited efficacy, however, in achieving parasitological cure.

Preferred Therapy for Acute, Early Chronic, and Re-Activated Disease:

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days **(BIII)** (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Alternative Therapy

- Nifurtimox 8–10 mg/kg/day PO for 90–120 days **(CIII)** (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Note:

* Optimal duration of therapy has not been studied in HIV-infected patients.
* Initiation or optimization of ART in patients undergoing treatment for Chagas disease, once the patient is clinically stable **(AIII)**
* Even with treatment, mortality is high in patients with symptomatic reactivation.

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; PO = orally

References

1. Bittencourt AL. Congenital Chagas disease. *Am J Dis Child*. Jan 1976;130(1):97-103. Available at http://www.ncbi.nlm.nih.gov/pubmed/813519.
2. Maguire J. Trypanosomoa. In: Gorbach S. BJ, Blacklow, N; ed. *Infectious Diseases*: Lippincott, Williams & Wilkins; 2004:2327-2334.
3. Benchimol Barbosa PR. The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks. *Int J Cardiol*. Sep 10 2006;112(1):132-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/16600406.
4. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. Apr 17 2010;375(9723):1388-1402. Available at http://www.ncbi.nlm.nih.gov/pubmed/20399979.
5. Organización Panamericana de la Salud. Estimación cuantativa de la enfermedad de Chagas en las Américas. Montevideo, Uraguay, Organización Panamericana de la Salud. 2006.
6. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop*. Jul-Aug 2010;115(1-2):22-27. Available at http://www.ncbi.nlm.nih.gov/pubmed/19646412.
7. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz*. Jul 2003;98(5):577-591. Available at http://www.ncbi.nlm.nih.gov/pubmed/12973523.
8. Dorn PL, Perniciaro L, Yabsley MJ, et al. Autochthonous transmission of Trypanosoma cruzi, Louisiana. *Emerg Infect Dis*. Apr 2007;13(4):605-607. Available at http://www.ncbi.nlm.nih.gov/pubmed/17553277.
9. Herwaldt BL, Grijalva MJ, Newsome AL, et al. Use of polymerase chain reaction to diagnose the fifth reported US case of autochthonous transmission of Trypanosoma cruzi, in Tennessee, 1998. *J Infect Dis*. Jan 2000;181(1):395-399. Available at http://www.ncbi.nlm.nih.gov/pubmed/10608796.
10. Kjos SA, Snowden KF, Craig TM, Lewis B, Ronald N, Olson JK. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. Apr 15 2008;152(3-4):249-256. Available at http://www.ncbi.nlm.nih.gov/pubmed/18255233.
11. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for Pneumocystis carinii infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/2860516.
12. Centers for Disease C, Prevention. Blood donor screening for chagas disease--United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. Feb 23 2007;56(7):141-143. Available at http://www.ncbi.nlm.nih.gov/pubmed/17318113.
13. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. *Curr Opin Infect Dis*. Oct 2008;21(5):476-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/18725796.
14. Bern C, Verastegui M, Gilman RH, et al. Congenital Trypanosoma cruzi transmission in Santa Cruz, Bolivia. *Clin Infect Dis*. Dec 1 2009;49(11):1667-1674. Available at http://www.ncbi.nlm.nih.gov/pubmed/19877966.
15. Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. Mar 1994;50(3):261-268. Available at http://www.ncbi.nlm.nih.gov/pubmed/8147485.
16. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol*. Jan 2007;101(1):31-50. Available at http://www.ncbi.nlm.nih.gov/pubmed/17244408.
17. Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid Biol Dis*. May 13 2004;3(1):2. Available at http://www.ncbi.nlm.nih.gov/pubmed/15142278.
18. Committee WHOE. Control of Chagas disease. *World Health Organ Tech Rep Ser*. 2002;905:i-vi, 1-109, back cover. Available at http://www.ncbi.nlm.nih.gov/pubmed/12092045.
19. Rassi A, Jr., Rassi A, Little WC. Chagas' heart disease. *Clin Cardiol*. Dec 2000;23(12):883-889. Available at http://www.ncbi.nlm.nih.gov/pubmed/11129673.
20. Rassi A, Jr., Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol*. Jan 2001;76(1):75-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/11175486.
21. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroenterol*. Jun 1998;93(6):884-889. Available at http://www.ncbi.nlm.nih.gov/pubmed/9647012.
22. Campos SV, Strabelli TM, Amato Neto V, et al. Risk factors for Chagas' disease reactivation after heart transplantation. *J Heart Lung Transplant*. Jun 2008;27(6):597-602. Available at http://www.ncbi.nlm.nih.gov/pubmed/18503957.

23. Kohl S, Pickering LK, Frankel LS, Yaeger RG. Reactivation of Chagas' disease during therapy of acute lymphocytic leukemia. *Cancer*. Sep 1 1982;50(5):827-828. Available at http://www.ncbi.nlm.nih.gov/pubmed/6807527.

24. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis*. Sep 1999;29(3):561-567. Available at http://www.ncbi.nlm.nih.gov/pubmed/10530448.

25. Sartori AM, Neto JE, Nunes EV, et al. Trypanosoma cruzi parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. *J Infect Dis*. Sep 15 2002;186(6):872-875. Available at http://www.ncbi.nlm.nih.gov/pubmed/12198628.

26. Sartori AM, Lopes MH, Benvenuti LA, et al. Reactivation of Chagas' disease in a human immunodeficiency virus-infected patient leading to severe heart disease with a late positive direct microscopic examination of the blood. *Am J Trop Med Hyg*. Nov 1998;59(5):784-786. Available at http://www.ncbi.nlm.nih.gov/pubmed/9840598.

27. Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992-2007. *Int J Infect Dis*. Nov 2008;12(6):587-592. Available at http://www.ncbi.nlm.nih.gov/pubmed/18337139.

28. Diazgranados CA, Saavedra-Trujillo CH, Mantilla M, Valderrama SL, Alquichire C, Franco-Paredes C. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet Infect Dis*. May 2009;9(5):324-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/19393962.

29. Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, Rocha A. Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. *Clin Infect Dis*. Dec 1997;25(6):1397-1400. Available at http://www.ncbi.nlm.nih.gov/pubmed/9431385.

30. Leiby DA, Wendel S, Takaoka DT, Fachini RM, Oliveira LC, Tibbals MA. Serologic testing for Trypanosoma cruzi: comparison of radioimmunoprecipitation assay with commercially available indirect immunofluorescence assay, indirect hemagglutination assay, and enzyme-linked immunosorbent assay kits. *J Clin Microbiol*. Feb 2000;38(2):639-642. Available at http://www.ncbi.nlm.nih.gov/pubmed/10655360.

31. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gurtler RE. The challenges of Chagas Disease-- grim outlook or glimmer of hope. *PLoS Med*. Dec 2007;4(12):e332. Available at http://www.ncbi.nlm.nih.gov/pubmed/18162039.

32. Sosa-Estani S, Gamboa-Leon MR, Del Cid-Lemus J, et al. Use of a rapid test on umbilical cord blood to screen for Trypanosoma cruzi infection in pregnant women in Argentina, Bolivia, Honduras, and Mexico. *Am J Trop Med Hyg*. Nov 2008;79(5):755-759. Available at http://www.ncbi.nlm.nih.gov/pubmed/18981518.

33. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic Trypanosoma cruzi infection. *Am J Trop Med Hyg*. Mar 2009;80(3):410-415. Available at http://www.ncbi.nlm.nih.gov/pubmed/19270291.

34. Gorlin J, Rossmann S, Robertson G, et al. Evaluation of a new Trypanosoma cruzi antibody assay for blood donor screening. *Transfusion*. Mar 2008;48(3):531-540. Available at http://www.ncbi.nlm.nih.gov/pubmed/18067497.

35. Junqueira AC, Chiari E, Wincker P. Comparison of the polymerase chain reaction with two classical parasitological methods for the diagnosis of Chagas disease in an endemic region of north-eastern Brazil. *Trans R Soc Trop Med Hyg*. Mar-Apr 1996;90(2):129-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/8761570.

36. Wincker P, Telleria J, Bosseno MF, et al. PCR-based diagnosis for Chagas' disease in Bolivian children living in an active transmission area: comparison with conventional serological and parasitological diagnosis. *Parasitology*. Apr 1997;114 (Pt 4):367-373. Available at http://www.ncbi.nlm.nih.gov/pubmed/9107023.

37. Feilij H, Muller L, Gonzalez Cappa SM. Direct micromethod for diagnosis of acute and congenital Chagas' disease. *J Clin Microbiol*. Aug 1983;18(2):327-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/6413530.

38. Duffy T, Bisio M, Altcheh J, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. *PLoS Negl Trop Dis*. 2009;3(4):e419. Available at http://www.ncbi.nlm.nih.gov/pubmed/19381287.

39. Schijman AG, Vigliano C, Burgos J, et al. Early diagnosis of recurrence of Trypanosoma cruzi infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. *J Heart Lung Transplant*. Nov 2000;19(11):1114-1117. Available at http://www.ncbi.nlm.nih.gov/pubmed/11077230.

40. Qvarnstrom Y, Schijman AG, Veron V, Aznar C, Steurer F, da Silva AJ. Sensitive and specific detection of Trypanosoma cruzi DNA in clinical specimens using a multi-target real-time PCR approach. *PLoS Negl Trop Dis*. 2012;6(7):e1689. Available at http://www.ncbi.nlm.nih.gov/pubmed/22802973.

41. Mott KE, Muniz TM, Lehman JS, Jr., et al. House construction, triatomine distribution, and household distribution of

seroreactivity to Trypanosoma cruzi in a rural community in northeast Brazil. *Am J Trop Med Hyg*. Nov 1978;27(6):1116-1122. Available at http://www.ncbi.nlm.nih.gov/pubmed/103445.

42. Kroeger A, Villegas E, Ordonez-Gonzalez J, Pabon E, Scorza JV. Prevention of the transmission of Chagas' disease with pyrethroid-impregnated materials. *Am J Trop Med Hyg*. Mar 2003;68(3):307-311. Available at http://www.ncbi.nlm.nih.gov/pubmed/12685636.
43. Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. *Clin Microbiol Rev*. Jan 2005;18(1):12-29. Available at http://www.ncbi.nlm.nih.gov/pubmed/15653816.
44. Rodriques Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz*. Jan 2002;97(1):3-24. Available at http://www.ncbi.nlm.nih.gov/pubmed/11992141.
45. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. *JAMA*. Nov 14 2007;298(18):2171-2181. Available at http://www.ncbi.nlm.nih.gov/pubmed/18000201.
46. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). *Hum Exp Toxicol*. Aug 2006;25(8):471-479. Available at http://www.ncbi.nlm.nih.gov/pubmed/16937919.
47. Pinazo MJ, Espinosa G, Gallego M, Lopez-Chejade PL, Urbina JA, Gascon J. Successful treatment with posaconazole of a patient with chronic Chagas disease and systemic lupus erythematosus. *Am J Trop Med Hyg*. Apr 2010;82(4):583-587. Available at http://www.ncbi.nlm.nih.gov/pubmed/20348503.
48. Molina I, Gomez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med*. May 15 2014;370(20):1899-1908. Available at http://www.ncbi.nlm.nih.gov/pubmed/24827034.
49. Torrico F, Alonso-Vega C, Suarez E, et al. Maternal Trypanosoma cruzi infection, pregnancy outcome, morbidity, and mortality of congenitally infected and non-infected newborns in Bolivia. *Am J Trop Med Hyg*. Feb 2004;70(2):201-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/14993634.
50. Di Pentima MC, Hwang LY, Skeeter CM, Edwards MS. Prevalence of antibody to Trypanosoma cruzi in pregnant Hispanic women in Houston. *Clin Infect Dis*. Jun 1999;28(6):1281-1285. Available at http://www.ncbi.nlm.nih.gov/pubmed/10451166.
51. Edwards MS, Rench MA, Charles TW, et al. Perinatal Screening for Chagas Disease in Southern Texas. *J Ped Infect Dis*. 2015;4(1):67. Available at http://jpids.oxfordjournals.org/content/early/2013/10/03/jpids.pit056.1.full.
52. Bittencourt AL. Possible risk factors for vertical transmission of Chagas' disease. *Rev Inst Med Trop Sao Paulo*. Sep-Oct 1992;34(5):403-408. Available at http://www.ncbi.nlm.nih.gov/pubmed/1342103.
53. Scapellato PG, Bottaro EG, Rodriguez-Brieschke MT. Mother-child transmission of Chagas disease: could coinfection with human immunodeficiency virus increase the risk? *Rev Soc Bras Med Trop*. Mar-Apr 2009;42(2):107-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/19448923.
54. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis*. Sep 1995;21(3):551-555. Available at http://www.ncbi.nlm.nih.gov/pubmed/8527542.
55. Freilij H, Altcheh J, Muchinik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J*. Feb 1995;14(2):161-162. Available at http://www.ncbi.nlm.nih.gov/pubmed/7746707.
56. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Assessment of cytogenetic damage in chagasic children treated with benznidazole. *Mutat Res*. Oct 1988;206(2):217-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/3140001.
57. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res*. Oct 1989;224(2):263-267. Available at http://www.ncbi.nlm.nih.gov/pubmed/2507913.
58. de Toranzo EG, Masana M, Castro JA. Administration of benznidazole, a chemotherapeutic agent against Chagas disease, to pregnant rats. Covalent binding of reactive metabolites to fetal and maternal proteins. *Arch Int Pharmacodyn Ther*. Nov 1984;272(1):17-23. Available at http://www.ncbi.nlm.nih.gov/pubmed/6440493.
59. Correa VR, Barbosa FG, Melo Junior CA, D'Albuquerque e Castro LF, Andrade Junior HF, Nascimento N. Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report. *Rev Soc Bras Med Trop*. May-Jun 2014;47(3):397-400. Available at http://www.ncbi.nlm.nih.gov/pubmed/25075496.
60. Bisio M, Altcheh J, Lattner J, et al. Benznidazole treatment of chagasic encephalitis in pregnant woman with AIDS. *Emerg Infect Dis*. 2013;19(9):1490-1492. Available at http://www.ncbi.nlm.nih.gov/pubmed/23965334.
61. Oliveira I, Torrico F, Munoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. Aug 2010;8(8):945-956. Available at http://www.ncbi.nlm.nih.gov/pubmed/20695749.

Isosporiasis (Cystoisosporiasis) (Last updated September 10, 2015; last reviewed September 10, 2015)

Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.[1-7] Although *Isospora (Cystoisospora) belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.[2] Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.[6-12] Acalculous cholecystitis/cholangiopathy[2,13-15] and reactive arthritis[16] also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36 µm by 12–17 µm) in fecal specimens.[2] Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they autofluoresce.[2,17] Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.[2,10] Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.[2,18-20]

Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.[1,3,4,21] In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).[1] In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm^3.[3] After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in patients with versus without a history of Pneumocystis pneumonia—indirect evidence of a protective effect from use of TMP-SMX for Pneumocystis pneumonia.[4] Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isoporiasis-endemic areas.

Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients **(AIII)**. TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis **(AI)**. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails **(AIII)**.

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.[6,7,22] The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of the initial studies,[6,7] the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily **(AII)**.[23] In another study, TMP-SMX (160/800 mg) administered twice daily was also effective **(BI)**.[22] Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)[6,10] if symptoms worsen or persist **(BIII)**. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.[2,9,10,24-26] However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States **(CIII)**; it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,[27] and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.[3,28,29] Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients **(BIII)**.

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine.

Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.[3,14,21] Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent **(CI)**. On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.[22]

Unsubstantiated or mixed data are available for albendazole,[29-31] nitazoxanide,[32,33] doxycycline,[34] the macrolides roxithromycin and spiramycin,[25,35,36] and the veterinary anticoccidial agent diclazuril **(CIII)**.[37,38] Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.[8,25,26,28,35,37] Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm^3 should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections **(AI)**. In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.[6,7,22] In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) **(AI)**.[7] Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective **(BIII)**;[5,10] however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.[14]

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used **(BIII)**.[28] On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative **(CI)**.[22]

When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm^3 for >6 months after initiation of ART **(BIII)**.

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,[39-42] TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection **(CIII)**. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.[43] Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.[44]

Recommendations for Treating *Isospora belli* Infection

Treating *Isospora belli* Infection

General Management Considerations:

- Fluid and electrolyte support in patients with dehydration **(AIII)**
- Nutritional supplementation for malnourished patients **(AIII)**

Preferred Therapy for Acute Infection:

- TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days **(AII)**, *or*
- TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days **(BI)**
- One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist **(BIII)**
- IV therapy for patients with potential or documented malabsorption

Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):

- Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily **(BIII)**, *or*
- Ciprofloxacin 500 mg PO BID for 7 days **(CI)**

Chronic Maintenance Therapy (Secondary Prophylaxis)

(In Patients with CD4 Count <200/mm^3)

Preferred Therapy:

- TMP-SMX (160 mg/800 mg) PO 3 times weekly **(AI)**

Alternative Therapy:

- TMP-SMX (160 mg/800 mg) PO daily **(BIII)**, *or*
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly **(BIII)**, *or*
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)**
- Ciprofloxacin 500 mg PO 3 times weekly **(CI)** as a second line alternative

Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count >200 cells/mm^3 for >6 months in response to ART and without evidence of active *I. belli* infection **(BIII)**

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at http://www.ncbi.nlm.nih.gov/pubmed/10232311.
2. Lindsay DS, Dubey JP, Blagburn BL. Biology of Isospora spp. from humans, nonhuman primates, and domestic animals. *Clin Microbiol Rev*. Jan 1997;10(1):19-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/8993857.
3. Guiguet M, Furco A, Tattevin P, Costagliola D, Molina JM, French Hospital Database on HIVCEG. HIV-associated Isospora belli infection: incidence and risk factors in the French Hospital Database on HIV. *HIV Med*. Mar 2007;8(2):124-130. Available at http://www.ncbi.nlm.nih.gov/pubmed/17352769.
4. Sorvillo FJ, Lieb LE, Seidel J, Kerndt P, Turner J, Ash LR. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. *Am J Trop Med Hyg*. Dec 1995;53(6):656-659. Available at http://www.ncbi.nlm.nih.gov/pubmed/8561272.
5. Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. *Am J Trop Med Hyg*. Aug 2003;69(2):217-222. Available at http://www.ncbi.nlm.nih.gov/pubmed/13677379.
6. DeHovitz JA, Pape JW, Boncy M, Johnson WD, Jr. Clinical manifestations and therapy of Isospora belli infection in

patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Jul 10 1986;315(2):87-90. Available at http://www.ncbi.nlm.nih.gov/pubmed/3487730.

7. Pape JW, Verdier RI, Johnson WD, Jr. Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Apr 20 1989;320(16):1044-1047. Available at http://www.ncbi.nlm.nih.gov/pubmed/2927483.
8. Forthal DN, Guest SS. Isospora belli enteritis in three homosexual men. *Am J Trop Med Hyg*. Nov 1984;33(6):1060-1064. Available at http://www.ncbi.nlm.nih.gov/pubmed/6507724.
9. Modigliani R, Bories C, Le Charpentier Y, et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. *Gut*. Feb 1985;26(2):179-187. Available at http://www.ncbi.nlm.nih.gov/pubmed/4038492.
10. Whiteside ME, Barkin JS, May RG, Weiss SD, Fischl MA, MacLeod CL. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. Nov 1984;33(6):1065-1072. Available at http://www.ncbi.nlm.nih.gov/pubmed/6334448.
11. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: Nitazoxanide treatment failure in chronic isosporiasis. *Am J Trop Med Hyg*. Aug 2001;65(2):94-95. Available at http://www.ncbi.nlm.nih.gov/pubmed/11508398.
12. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated isospora belli diarrhea. *J Emerg Med*. Dec 2011;41(6):e129-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/18993015.
13. Benator DA, French AL, Beaudet LM, Levy CS, Orenstein JM. Isospora belli infection associated with acalculous cholecystitis in a patient with AIDS. *Ann Intern Med*. Nov 1 1994;121(9):663-664. Available at http://www.ncbi.nlm.nih.gov/pubmed/7944075.
14. Lagrange-Xelot M, Porcher R, Sarfati C, et al. Isosporiasis in patients with HIV infection in the highly active antiretroviral therapy era in France. *HIV Med*. Feb 2008;9(2):126-130. Available at http://www.ncbi.nlm.nih.gov/pubmed/18257775.
15. Walther Z, Topazian MD. Isospora cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. Sep 2009;40(9):1342-1346. Available at http://www.ncbi.nlm.nih.gov/pubmed/19447468.
16. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM, Jurado R, Torre-Cisneros J. Isospora belli reactive arthritis in a patient with AIDS. *Annals of the rheumatic diseases*. Sep 1994;53(9):618-619. Available at http://www.ncbi.nlm.nih.gov/pubmed/7979603.
17. Bialek R, Binder N, Dietz K, Knobloch J, Zelck UE. Comparison of autofluorescence and iodine staining for detection of Isospora belli in feces. *Am J Trop Med Hyg*. Sep 2002;67(3):304-305. Available at http://www.ncbi.nlm.nih.gov/pubmed/12408672.
18. Frenkel JK, Silva MB, Saldanha J, et al. Isospora belli infection: observation of unicellular cysts in mesenteric lymphoid tissues of a Brazilian patient with AIDS and animal inoculation. *The Journal of eukaryotic microbiology*. 2003;50 Suppl:682-684. Available at http://www.ncbi.nlm.nih.gov/pubmed/14736218.
19. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. *Am J Clin Pathol*. Apr 1987;87(4):536-542. Available at http://www.ncbi.nlm.nih.gov/pubmed/3826017.
20. Bernard E, Delgiudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 1997;16(9):699-701. Available at http://www.ncbi.nlm.nih.gov/pubmed/9352268.
21. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. Jun 2009;80(6):1060-1064. Available at http://www.ncbi.nlm.nih.gov/pubmed/19478276.
22. Verdier RI, Fitzgerald DW, Johnson WD, Jr., Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients. A randomized, controlled trial. *Ann Intern Med*. Jun 6 2000;132(11):885-888. Available at http://www.ncbi.nlm.nih.gov/pubmed/10836915.
23. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. Feb 1 2001;32(3):331-351. Available at http://www.ncbi.nlm.nih.gov/pubmed/11170940.
24. Mojon M, Coudert J, E.O. dL. Serious isosporosis by Isospora belli: a case report treated by Fansidar [Abstract]. *Southeast Asian J Trop Med Public Health*. 12:449-500. 1981.

25. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by Isospora belli: therapeutic response to pyrimethamine and sulfadiazine. *Diagn Microbiol Infect Dis*. Oct 1996;26(2):87-89. Available at http://www.ncbi.nlm.nih.gov/pubmed/8985661.

26. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. May 1974;66(5):923-935. Available at http://www.ncbi.nlm.nih.gov/pubmed/4826994.

27. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for Pneumocystis carinii infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/2860516.

28. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med*. Sep 15 1988;109(6):474-475. Available at http://www.ncbi.nlm.nih.gov/pubmed/3261956.

29. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scandinavian journal of infectious diseases*. 2002;34(11):859-862. Available at http://www.ncbi.nlm.nih.gov/pubmed/12578164.

30. Dionisio D, Sterrantino G, Meli M, Leoncini F, Orsi A, Nicoletti P. Treatment of isosporiasis with combined albendazole and ornidazole in patients with AIDS. *AIDS*. Sep 1996;10(11):1301-1302. Available at http://www.ncbi.nlm.nih.gov/pubmed/8883600.

31. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Alimentary pharmacology & therapeutics*. 2002; 16(3):595-601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11876715.

32. Romero Cabello R, Guerrero LR, Munoz Garcia MR, Geyne Cruz A. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg*. Nov-Dec 1997;91(6):701-703. Available at http://www.ncbi.nlm.nih.gov/pubmed/9580117.

33. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. Jun 1997;56(6):637-639. Available at http://www.ncbi.nlm.nih.gov/pubmed/9230795.

34. Meyohas MC, Capella F, Poirot JL, et al. [Treatment with doxycycline and nifuroxazide of Isospora belli infection in AIDS]. *Pathologie-biologie*. Jun 1990;38(5 (Pt 2)):589-591. Available at http://www.ncbi.nlm.nih.gov/pubmed/2385457.

35. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to Isospora belli with spiramycin: a case report. *J Infect Dis*. Dec 1985;152(6):1336-1338. Available at http://www.ncbi.nlm.nih.gov/pubmed/4067332.

36. Musey KL, Chidiac C, Beaucaire G, Houriez S, Fourrier A. Effectiveness of roxithromycin for treating Isospora belli infection. *J Infect Dis*. Sep 1988;158(3):646. Available at http://www.ncbi.nlm.nih.gov/pubmed/3411149.

37. Limson-Pobre RN, Merrick S, Gruen D, Soave R. Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis*. Jan 1995;20(1):201-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/7727660.

38. Kayembe K, Desmet P, Henry MC, Stoffels P. Diclazuril for Isospora belli infection in AIDS. *Lancet*. Jun 17 1989;1(8651):1397-1398. Available at http://www.ncbi.nlm.nih.gov/pubmed/2567420.

39. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at http://www.ncbi.nlm.nih.gov/pubmed/11738517.

40. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at http://www.ncbi.nlm.nih.gov/pubmed/11096168.

41. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *American journal of epidemiology*. May 15 2001;153(10):961-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/11384952.

42. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sexually transmitted infections*. Dec 2001;77(6):441-443. Available at http://www.ncbi.nlm.nih.gov/pubmed/11714944.

43. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. Jul-Aug 2001;95(4):424-428. Available at http://www.ncbi.nlm.nih.gov/pubmed/11579889.

44. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. May 2006;107(5):1120-1138. Available at http://www.ncbi.nlm.nih.gov/pubmed/16648419.

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 1 of 5)

(Last updated May 18, 2017; last reviewed May 18, 2017)

Opportunistic Infections	Indication	Preferred	Alternative
***Pneumocystis* pneumonia (PCP)**	• CD4 count <200 cells/mm^3 **(AI)**, *or* • Oropharyngeal candidiasis **(AII)**, *or* • CD4 <14% **(BII)**, *or* • History of AIDS-defining illness **(BII)**, *or* • CD4 count >200 but <250 cells/mm^3 if monitoring CD4 cell count every 3 months is not possible **(BII)** **Note:** Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis **(AII)**.	• TMP-SMX[a] 1 double-strength (DS) PO daily **(AI)**, *or* • TMP-SMX[a] 1 single-strength (SS) daily **(AI)**	• TMP-SMX[a] 1 DS PO three times weekly **(BI)**, *or* • Dapsone[b] 100 mg PO daily or 50 mg PO BID **(BI)**, *or* • Dapsone[b] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)**, *or* • (Dapsone[b] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)**; *or* • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month **(BI)**, *or* • Atovaquone 1500 mg PO daily **(BI)**, *or* • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**
***Toxoplasma gondii* encephalitis**	• Toxoplasma IgG-positive patients with CD4 count <100 cells/µL **(AII)**; • Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have toxoplasma serology retested if CD4 count decline to <100 cells/µL **(CIII)**. Prophylaxis should be initiated if seroconversion occurred **(AII)**. **Note:** All regimens recommended for primary prophylaxis against toxoplasmosis are also effective as PCP prophylaxis.	TMP-SMX[a] 1 DS PO daily **(AII)**	• TMP-SMX[a] 1 DS PO three times weekly **(BIII)**, *or* • TMP-SMX[a] 1 SS PO daily **(BIII)**, *or* • Dapsone[b] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)**, *or* • (Dapsone[b] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)**; *or* • Atovaquone 1500 mg PO daily **(CIII)**; *or* • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**
***Mycobacterium tuberculosis* infection (TB)** (i.e., treatment of latent TB infection [LTBI])	• (+) screening test for LTBI[d], with no evidence of active TB, and no prior treatment for active TB or LTBI **(AI)**, *or* • Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results **(AII)**.	• (INH 300 mg + pyridoxine 25–50 mg) PO daily x 9 months **(AII)**, *or* • NH 900 mg PO BIW (by DOT) + pyridoxine 25–50 mg PO daily x 9 months **(BII)**.	• Rifampin 600 mg PO daily x 4 months **(BIII)**, *or* • Rifabutin (dose adjusted based on concomitant ART)[e] x 4 months **(BIII)**, *or* • [Rifapentine (see dose below) PO + INH 900 mg PO + pyridoxine 50 mg PO] once weekly x 12 weeks *rifapentine dose:* • 32.1 to 49.9 kg: 750 mg • 50 mg: 900 mg Rifapentine only recommended for patients receiving raltegravir or efavirenz-based ART regimen For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities **(AII)**.

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 2 of 5)

Opportunistic Infections	Indication	Preferred	Alternative
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4 count <50 cells/μL—after ruling out active disseminated MAC disease based on clinical assessment **(AI)**.	• Azithromycin 1200 mg PO once weekly **(AI)**, *or* • Clarithromycin 500 mg PO BID **(AI)**, *or* • Azithromycin 600 mg PO twice weekly **(BIII)**	Rifabutin (dose adjusted based on concomitant ART)[e] **(BI)**; rule out active TB before starting rifabutin.
***Streptococcus pneumoniae* infection**	For individuals who have not received any pneumococcal vaccine, regardless of CD4 count, followed by: • if CD4 count ≥200 cells/μL • if CD4 count <200 cells/μL	PCV13 0.5 mL IM x 1 **(AI)**. PPV23 0.5 mL IM or SQ at least 8 weeks after the PCV13 vaccine **(AII)**. PPV23 can be offered at least 8 weeks after receiving PCV13 **(CIII)** or can wait until CD4 count increased to ≥200 cells/μL **(BIII)**.	PPV23 0.5 mL IM or SQ x 1 **(BII)**
	For individuals who have previously received PPV23	One dose of PCV13 should be given at least 1 year after the last receipt of PPV23 **(AII)**.	
	<u>Re-vaccination</u> • If age 19–64 years and ≥5 years since the first PPV23 dose • If age ≥65 years, and if ≥5 years since the previous PPV23 dose	• PPV23 0.5 mL IM or SQ x 1 **(BIII)** • PPV23 0.5 mL IM or SQ x 1 **(BIII)**	
Influenza A and B virus infection	All HIV-infected patients **(AIII)**	Inactivated influenza vaccine annually (per recommendation for the season) **(AIII)** Live-attenuated influenza vaccine is **<u>contraindicated</u>** in HIV-infected patients **(AIII)**.	
Syphilis	• For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within past 90 days **(AII)**, *or* • For individuals exposed to a sex partner >90 days before syphilis diagnosis in the partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain **(AIII)**	Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)**	*For penicillin-allergic patients:* • Doxycycline 100 mg PO BID for 14 days **(BII)**, *or* • Ceftriaxone 1 g IM or IV daily for 8–10 days **(BII)**, *or* • Azithromycin 2 g PO for 1 dose **(BII)** – **<u>not recommended</u>** for MSM or pregnant women **(AII)**
***Histoplasma capsulatum* infection**	CD4 count ≤150 cells/μL and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**	Itraconazole 200 mg PO daily **(BI)**	

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 3 of 5)

Opportunistic Infections	Indication	Preferred	Alternative
Coccidioidomycosis	A new positive IgM or IgG serologic test in patients who live in a disease-endemic area and with CD4 count <250 cells/μL **(BIII)**	Fluconazole 400 mg PO daily **(BIII)**	
Varicella-zoster virus (VZV) infection	Pre-exposure prevention: Patients with CD4 counts ≥200 cells/μL who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV **(CIII)** **Note:** Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended. Post-exposure prevention: **(AIII)** Close contact with a person with chickenpox or herpes zoster; and is susceptible (i.e., no history of vaccination or of either condition, or known to be VZV seronegative)	Pre-exposure prevention: Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ each) administered 3 months apart **(CIII)**. If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)**. Post-exposure prevention: Varicella-zoster immune globulin (VariZIG™) 125 international units per 10 kg (maximum 625 international units) IM, administered as soon as possible and within 10 days after exposure **(AIII)** **Note:** VariZIG is exclusively distributed by FFF Enterprises at 800-843-7477. Individuals receiving monthly high-dose IVIG (>400 mg/kg) are likely to be protected if the last dose of IVIG was administered <3 weeks before exposure.	Pre-exposure prevention: VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts **(BIII)**. Alternative post-exposure prevention: • Acyclovir 800 mg PO 5 x/day for 5–7 days **(BIII)**, *or* • Valacyclovir 1 g PO TID for 5–7 days **(BIII)** These alternatives have not been studied in the HIV population. If antiviral therapy is used, varicella vaccines should not be given until at least 72 hours after the last dose of the antiviral drug.
Human Papillomavirus (HPV) infection	Females aged 13–26 years **(BIII)**	• HPV quadrivalent vaccine 0.5 mL IM at months 0, 1–2, and 6 **(BIII)**, *or* • HPV bivalent vaccine 0.5 mL IM at months 0, 1–2, and 6 **(BIII)**, *or* • HPV 9-valent vaccine 0.5 mL IM at months 0, 1–2, and 6 **(BIII)**	
	Males aged 13–26 years **(BIII)**	• HPV quadrivalent vaccine 0.5 mL IM at months 0, 1–2, and 6 **(BIII)**, *or* • HPV 9-valent vaccine 0.5 mL IM at months 0, 1–2, and 6 **(BIII)**	

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 4 of 5)

Opportunistic Infections	Indication	Preferred	Alternative
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease, or who are injection-drug users, or MSM **(AII)**.	Hepatitis A vaccine 1 mL IM x 2 doses at 0 and 6–12 months **(AII)**. IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated when CD4 count >200 cells/µL. **(BIII)**.	For patients susceptible to both HAV and hepatitis B virus (HBV) infection (see below): Combined HAV and HBV vaccine (Twinrix®), 1 mL IM as a 3-dose (0, 1, and 6 months) or 4-dose series (days 0, 7, 21 to 30, and 12 months) **(AII)**
Hepatitis B virus (HBV) infection	• Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs <10 international units/mL) **(AII)** • Patients with isolated anti-HBc and negative HBV DNA **(BII)** • Early vaccination is recommended before CD4 count falls below 350 cells/µL **(AII)**. • However, in patients with low CD4 cell counts, vaccination should not be deferred until CD4 count reaches >350 cells/µL, because some patients with CD4 counts <200 cells/µL do respond to vaccination **(AII)**.	• HBV vaccine IM (Engerix-B 20 µg/mL or Recombivax HB 10 µg/mL), 0, 1, and 6 months **(AII)**, *or* • HBV vaccine IM (Engerix-B 40 µg/mL or Recombivax HB 20 µg/mL) 0, 1, 2 and 6 months **(BI)**, *or* • Combined HAV and HBV vaccine (Twinrix®), 1 mL IM as a 3-dose (0, 1, and 6 months) or 4-dose series (days 0, 7, 21 to 30, and 12 months) **(AII)** Anti-HBs should be obtained 1 month after completion of the vaccine series. Patients with anti-HBs <10 international units/mL at 1 month are considered non-responders **(BIII)**.	Some experts recommend vaccinating with 40-µg doses of either HBV vaccine **(CIII)**.
	Vaccine Non-Responders: • Anti-HBs <10 international units/mL 1 month after vaccination series • For patients with low CD4 counts at time of first vaccine series, some experts might delay re-vaccination until after a sustained increase in CD4 count with ART **(CIII)**.	Re-vaccinate with a second vaccine series **(BIII)**	• HBV vaccine IM (Engerix-B 40 µg/mL or Recombivax HB 20 µg/mL), 0, 1, 2 and 6 months **(BI)**.
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on region of travel, malaria risks, and drug susceptibility in the region. Refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/.	

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 5 of 5)

Opportunistic Infections	Indication	Preferred	Alternative
Penicilliosis	Patients with CD4 cell counts <100 cells/μL who live or stay for a long period in rural areas in northern Thailand, Vietnam, or Southern China **(BI)**	Itraconazole 200 mg once daily **(BI)**	Fluconazole 400 mg PO once weekly **(BII)**

Key to Acronyms: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; BID = twice daily; BIW = twice a week; CD4 = CD4 T lymphocyte cell; DOT = directly observed therapy; DS = double strength; HAV = hepatitis A virus; HBV = hepatitis B virus; HPV = human papillomavirus; IgG = immunoglobulin G; IgM = immunoglobulin M; IM = intramuscular; INH = isoniazid; IV= intravenously; IVIG = intravenous immunoglobulin; LTBI = latent tuberculosis infection; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine; PO = orally; PPV23 = 23-valent pneumococcal polysaccharides vaccine; SQ = subcutaneous; SS = single strength; TB = tuberculosis; TMP-SMX = Trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

[a] TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection

[b] Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) before administration of dapsone or primaquine. Alternative agent should be used in patients found to have G6PD deficiency

[c] Screening tests for LTBI include tuberculin skin test (TST) or interferon-gamma release assays (IGRA)

[d] Refer to the Drug Interactions section in the Adult and Adolescent ARV Guidelines for dosing recommendation

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Evidence Rating:

Strength of Recommendation:

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III: Expert opinion

In cases where there are no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected patients exist that can plausibly guide management decisions for patients with HIV/AIDS, the data will be rated as III but will be assigned recommendations of A, B, C depending on the strength of recommendation.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 1 of 22) (Last updated May 18, 2017; last reviewed May 18, 2017)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***Pneumocystis* Pneumonia (PCP)**	Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX **(BIII)**. Duration of PCP treatment: 21 days **(AII)** For Moderate-to-Severe PCP: • TMP-SMX: [TMP 15–20 mg and SMX 75–100 mg]/kg/day IV given q6h or q8h **(AI)**, may switch to PO after clinical improvement **(AI)** For Mild-to-Moderate PCP: • TMP-SMX: [TMP 15–20 mg and SMX 75–100 mg]/kg/day, given PO in 3 divided doses **(AI)**, *or* • TMP-SMX: (160 mg/800 mg or DS) 2 tablets PO TID **(AI)** Secondary Prophylaxis, after completion of PCP treatment: • TMP-SMX DS: 1 tablet PO daily **(AI)**, *or* • TMP-SMX (80 mg/400 mg or SS): 1 tablet PO daily **(AI)**	For Moderate-to-Severe PCP: • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes **(AI)**; can reduce dose to 3 mg/kg IV daily because of toxicities **(BI)**, *or* • Primaquine 30 mg (base) PO daily + (clindamycin 600 mg q6h IV or 900 mg IV q8h) or (clindamycin 450 mg PO q6h or 600 mg PO q8h) **(AI)** For Mild-to-Moderate PCP: • Dapsone 100 mg PO daily + TMP 5 mg/kg PO TID **(BI)**, *or* • Primaquine 30 mg (base) PO daily + (clindamycin 450 mg PO q6h or 600 mg PO q8h) **(BI)**, *or* • Atovaquone 750 mg PO BID with food **(BI)** Secondary Prophylaxis, after completion of PCP treatment: • TMP-SMX DS: 1 tablet PO three times weekly **(BI)**, *or* • Dapsone 100 mg PO daily **(BI)**, *or* • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)**, *or* • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)**, *or* • Aerosolized pentamidine 300 mg monthly via Respirgard II™ nebulizer **(BI)**, *or* • Atovaquone 1500 mg PO daily **(BI)**, *or* • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**	Indications for Adjunctive Corticosteroids **(AI)**: • PaO_2 <70 mmHg at room air, *or* • Alveolar-arterial O_2 gradient >35 mmHg Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) **(AI)**: • Days 1–5: 40 mg PO BID • Days 6–10: 40 mg PO daily • Days 11–21: 20 mg PO daily IV methylprednisolone can be administered as 75% of prednisone dose. Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP **(BIII)**. Whenever possible, patients should be tested for G6PD before use of dapsone or primaquine. Alternative therapy should be used in patients found to have G6PD deficiency. Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis **(AII)**. If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction resolves **(AII)**. The dose can be increased gradually (desensitization) **(BI)**, reduced, or the frequency modified **(CIII)**. TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrosis **(AII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 2 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments

Toxoplasma gondii **Encephalitis**	Treatment of Acute Infection **(AI)**:
	• Pyrimethamine 200 mg PO 1 time, followed by weight-based therapy:
	  • If <60 kg, pyrimethamine 50 mg PO once daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO once daily
	  • If ≥60 kg, pyrimethamine 75 mg PO once daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO once daily
	• Leucovorin dose can be increased to 50 mg daily or BID.
	
	Duration for Acute Therapy:
	• At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
	• After completion of acute therapy, all patients should be initated on chronic maintenance therapy
	
	Chronic Maintenance Therapy:
	• Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses) + leucovorin 10–25 mg PO daily **(AI)**
		Treatment of Acute Infection:
		• Pyrimethamine (leucovorin)* + clindamycin 600 mg IV or PO q6h **(AI)**, *or*
		• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO BID **(BI)**, *or*
		• Atovaquone 1500 mg PO BID with food + pyrimethamine (leucovorin)* **(BII)**, *or*
		• Atovaquone 1500 mg PO BID with food + sulfadiazine 1000–1500 mg PO q6h (weight-based dosing, as in preferred therapy) **(BII)**, *or*
		• Atovaquone 1500 mg PO BID with food **(BII)**, *or*
		• Pyrimethamine (leucovorin)* + azithromycin 900–1200 mg PO daily **(CII)**
		
		Chronic Maintenance Therapy:
		• Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily **(BI)**, *or*
		• TMP-SMX DS 1 tablet BID **(BII)**, *or*
		• TMP-SMX DS 1 tablet once daily **(BII)**; *or*
		• Atovaquone 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(BII)**, *or*
		• Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses **[BII])**, *or*
		• Atovaquone 750–1500 mg PO BID with food **(BII)**
		
		* Pyrimethamine and leucovorin doses are the same as for preferred therapy.
			If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine **(BI)**.
			
			For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies **(BI)**
			
			Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved **(CIII)**.
			
			Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema **(BIII)**; discontinue as soon as clinically feasible.
			
			Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continued through acute treatment, but should not be used as seizure prophylaxis **(AIII)**.
			
			If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP **(AII)**.

Cryptosporidiosis	• Initiate or optimize ART for immune restoration to CD4 count >100 cells/μL **(AII)**, *and* • Aggressive oral or IV rehydration and replacement of electrolyte loss **(AIII)**, *and* • Symptomatic treatment of diarrhea with anti-motility agents **(AIII)**.	No therapy has been shown to be effective without ART. Trial of these agents may be used in conjunction with, but not instead of, ART: • Nitazoxanide 500–1000 mg PO BID for 14 days **(CIII)**, *or* • Paromomycin 500 mg PO QID for 14–21 days **(CIII)** • With optimized ART, symptomatic treatment and rehydration and electrolyte replacement	Tincture of opium may be more effective than loperamide in management of diarrhea **(CII).**

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 3 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Microsporidiosis	For GI Infections Caused by *Enterocytozoon bienuesi*: • Initiate or optimize ART as immune restoration to CD4 count >100 cells/μL **(AII)**; *plus* • Manage severe dehydration, malnutrition, and wasting by fluid support **(AII)** and nutritional supplement **(AIII)** For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than *E. bienuesi* and *Vittaforma corneae*: • Albendazole 400 mg PO BID **(AII)**, continue until CD4 count >200 cells/μL for >6 months after initiation of ART **(BIII)** For Ocular Infection: • Topical fumagillin bicylohexylammonium (Fumidil B) eye drops: 3 mg/mL in saline (fumagillin 70 μg/mL)—2 drops q2h for 4 days, then 2 drops QID (investigational use only in United States) **(BII)** + albendazole 400 mg PO BID, for management of systemic infection **(BIII)** • Therapy should be continued until resolution of ocular symptoms and CD4 count increase to >200 cells/μL for >6 months in response to ART **(CIII)**.	For GI Infections Caused by *E. bienuesi*: • Fumagillin 60 mg/day **(BII)** and TNP-470 (a synthetic analog of fumagillin) **(BIII)** may be effective, but neither is available in the United States. • Nitazoxanide (1000 mg BID) may have some effect but response may be minimal in patients with low CD4 cell counts **(CIII)**. For Disseminated Disease Attributed to *Trachipleistophora* or *Anncaliia*: • Itraconazole 400 mg PO daily + albendazole 400 mg PO BID **(CIII)**	Anti-motility agents can be used for diarrhea control if required **(BIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 4 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***Mycobacterium tuberculosis* (TB) Disease**	After collecting specimen for culture and molecular diagnostic tests, empiric TB treatment should be started in individuals with clinical and radiographic presentation suggestive of TB **(AIII)**. *Refer to Table 3 for dosing recommendations.* Initial Phase (2 Months, Given Daily, 5–7 Times/Week by DOT) **(AI)**: • INH + [RIF or RFB] + PZA + EMB **(AI)**, Continuation Phase: • INH + (RIF or RFB) daily (5–7 times/week) **(AIII)** Total Duration of Therapy (For Drug-Susceptible TB): • Pulmonary drug-susceptible TB: 6 months **(BII)** • Pulmonary TB and culture-positive after 2 months of TB treatment: 9 months **(BII)** • Extra-pulmonary TB w/CNS infection: 9–12 months **(BII)**; • Extra-pulmonary TB w/bone or joint involvement: 6 to 9 months **(BII)**; • Extra-pulmonary TB in other sites: 6 months **(BII)** Total duration of therapy should be based on number of doses received, not on calendar time	**Treatment for Drug-Resistant TB** Resistant to INH: • (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months **(BII)**; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months **(BII)** Resistant to Rifamycins +/- Other Drugs: • Regimen and duration of treatment should be individualized based on resistance pattern, clinical and microbiological responses, and in close consultation with experienced specialists **(AIII)**.	Adjunctive corticosteroid improves survival for TB meningitis and pericarditis **(AI)**. See text for drug, dose, and duration recommendations. All rifamycins may have significant pharmacokinetic interactions with antiretroviral drugs, please refer to the Drug Interactions section in the Adult and Adolescent ARV Guidelines for dosing recommendations. Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART. Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy **(BIII)**. For severe IRIS reaction, consider prednisone and taper over 4 weeks based on clinical symptoms **(BIII)**. For example: • If receiving RIF: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks • If receiving RFB: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks A more gradual tapering schedule over a few months may be necessary for some patients.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 5 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Disseminated *Mycobacterium avium* Complex (MAC) Disease	At Least 2 Drugs as Initial Therapy With: • Clarithromycin 500 mg PO BID **(AI)** + ethambutol 15 mg/kg PO daily **(AI)**, *or* • (Azithromycin 500–600 mg + ethambutol 15 mg/kg) PO daily **(AII)** if drug interaction or intolerance precludes the use of clarithromycin Duration: • At least 12 months of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/μL in response to ART	Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 counts <50 cells/μL), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**. Third or Fourth Drug Options May Include: • RFB 300 mg PO daily (dosage adjustment may be necessary based on drug interactions) **(CI)**, • Amikacin 10–15 mg/kg IV daily **(CIII)** or Streptomycin 1 g IV or IM daily **(CIII)**], *or* • Moxifloxacin 400 mg PO daily **(CIII)** or Levofloxacin 500 mg PO daily **(CIII)**	Testing of susceptibility to clarithromycin and azithromycin is recommended **(BIII)**. NSAIDs can be used for patients who experience moderate to severe symptoms attributed to IRIS **(CIII)**. If IRIS symptoms persist, short-term (4–8 weeks) systemic corticosteroids (equivalent to 20–40 mg prednisone) can be used **(CII)**.
Bacterial Respiratory Diseases *(with focus on pneumonia)*	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available **(BIII)**.		Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated. Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance **(BIII)**. Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications. Chemoprophylaxis can be considered for patients with frequent recurrences of serious bacterial pneumonia **(CIII)**. Clinicians should be cautious about using antibiotics to prevent recurrences because of the potential for developing drug resistance and drug toxicities.

	Empiric Outpatient Therapy:
	• A PO beta-lactam + a PO macrolide (azithromycin or clarithromycin) **(AII)**
	  • *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
	  • *Alternative beta-lactams:* cefpodoxime or cefuroxime, *or*
	• *For penicillin-allergic patients:* Levofloxacin 750 mg PO once daily **(AII)**, or moxifloxacin 400 mg PO once daily **(AII)**
	Duration: 7–10 days (a minimum of 5 days). Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics.
	Empiric Therapy for Non-ICU Hospitalized Patients:
	• An IV beta-lactam + a macrolide (azithromycin or clarithromycin) **(AII)**
	  • *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
	• *For penicillin-allergic patients:* Levofloxacin, 750 mg IV once daily **(AII)**, or moxifloxacin, 400 mg IV once daily **(AII)**
		Empiric Outpatient Therapy:
		• A PO beta-lactam + PO doxycycline **(CIII)**
		  • *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
		  • *Alternative beta-lactams:* cefpodoxime or cefuroxime
		Empiric Therapy for Non-ICU Hospitalized Patients:
		• An IV beta-lactam + doxycycline **(CIII)**
		Empiric Therapy For ICU Patients:
		• *For penicillin-allergic patients:* Aztreonam IV + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)**
		Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia:
		• An IV antipneumococcal, antipseudomonal beta-lactam + an aminoglycoside + azithromycin **(BIII)**, *or*
		• Above beta-lactam + an aminoglycoside + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)**, *or*
		• *For penicillin-allergic patients:* Replace the beta-lactam with aztreonam **(BIII)**.	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 6 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments

Bacterial Respiratory Diseases *(with focus on pneumonia)*, continued	Empiric Therapy for ICU Patients:
	• An IV beta-lactam + IV azithromycin **(AII)**, *or*
	• An IV beta-lactam + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(AII)**
	  • *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
	
	Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia:
	• An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin 400 mg IV q8–12h or levofloxacin 750 mg IV once daily) **(BIII)**
	  • *Preferred beta-lactams:* piperacillin-tazobactam, cefepime, imipenem, or meropenem
	
	Empiric Therapy for Patients at Risk for Methicillin-Resistant *Staphylococcus aureus* Pneumonia:
	• Add vancomycin IV or linezolid (IV or PO) to the baseline regimen **(BIII)**.
	• Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CIII)**.		

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 7 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections: *Empiric Therapy pending definitive diagnosis.*	Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. Empiric antibiotic therapy is indicated for patients with advanced HIV (CD4 count <200 cells/μL or concomitant AIDS-defining illnesses), with clinically severe diarrhea (≥ 6 stools per day or bloody stool) and/or accompanying fever or chills. Empiric Therapy: • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)** Therapy should be adjusted based on the results of diagnostic work-up. For patients with chronic diarrhea (>14 days) without severe clinical signs, empiric antibiotics therapy is not necessary, can withhold treatment until a diagnosis is made.	Empiric Therapy: • Ceftriaxone 1 g IV q24h **(BIII)**, *or* • Cefotaxime 1 g IV q8h **(BIII)**	Hospitalization with IV antibiotics should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, and blood pressure instability. Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium-difficile*-associated diarrhea **(BIII)**. If no clinical response after 5–7 days, consider follow-up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing), alternative diagnosis, or antibiotic resistance.
Salmonellosis	All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20-100 fold) and mortality (by up to 7-fold) compared to HIV-negative individuals **(AIII)**.		Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided **(BIII)**. The role of long-term secondary prophylaxis in patients with recurrent *Salmonella* bacteremia is not well established. Must weigh benefit against risks of long-term antibiotic exposure **(CIII)**. Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.
	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h, if susceptible **(AIII)** Duration of Therapy: *For gastroenteritis without bacteremia:* • If CD4 count ≥200 cells/μL: 7–14 days **(BIII)** • If CD4 count <200 cells/μL: 2–6 weeks **(CIII)** *For gastroenteritis with bacteremia:* • If CD4 count ≥200/μL: 14 days **(AIII)**; longer duration if bacteremia persists or if the infection is complicated (e.g., if metastatic foci of infection are present) **(BIII)** • If CD4 count <200 cells/μL: 2–6 weeks **(CIII)** Secondary Prophylaxis Should Be Considered For: • Patients with recurrent *Salmonella* gastroenteritis +/- bacteremia **(CIII)**, *or* • Patients with CD4 <200 cells/μL with severe diarrhea **(CIII)**	• Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or* • Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**, *or* • TMP, 160 mg-SMX 800 mg (PO or IV) q12h **(BIII)**, *or* • Ceftriaxone 1 g IV q24h **(BIII)**, *or* • Cefotaxime 1 g IV q8h **(BIII)**	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 8 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Shigellosis	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)** Duration of Therapy: • *Gastroenteritis:* 7–10 days **(AIII)** • *Bacteremia:* ≥14 days **(BIII)** • *Recurrent Infections:* 2–6 weeks **(BIII)**	• Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or* • Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**, *or* • TMP 160 mg-SMX 800 mg (PO or IV) q12h **(BIII)** (Note: *Shigella* infections acquired outside of the United States have high rates of TMP-SMX resistance), *or* • Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: not recommended for patients with bacteremia **[AIII]**)	Therapy is indicated both to shorten duration of illness and prevent spread of infection **(AIII)**. Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided **(BIII)**. If no clinical response after 5–7 days, consider follow-up stool culture, alternative diagnosis, or antibiotic resistance. Effective ART may reduce the frequency, severity, and recurrence of *shigella* infections.
Campylobacteriosis	For Mild Disease and If CD4 Count >200 cells/μL: • Withhold therapy unless symptoms persist for more than several days **(CIII)** For Mild-to-Moderate Disease (If Susceptible): • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)**, *or* • Azithromycin 500 mg PO daily **(BIII)** (Note: Not for patients with bacteremia) For *Campylobacter* Bacteremia: • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)** + an aminoglycoside **(BIII)**. Duration of Therapy: • *Gastroenteritis:* 7–10 days **(AIII)** (5 days with azithromycin) • *Bacteremia:* ≥14 days **(BIII)** • *Recurrent bacteremia:* 2–6 weeks **(BIII)**	For Mild-to-Moderate Disease (If Susceptible): • Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or* • Moxifloxacin 400 mg (PO or IV) q24h **(BIII)** Add an aminoglycoside to fluoroquinolone in bacteremic patients **(BIII)**.	Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided **(BIII)**. If no clinical response after 5–7 days, consider follow-up stool culture, alternative diagnosis, or antibiotic resistance. There is an increasing rate of fluoroquinolone resistance in the United States (24% resistance in 2011). The rationale for addition of aminoglycoside to a fluoroquinolone in bacteremic patients is to prevent emergence of quinolone resistance. Antimicrobial therapy should be modified based on susceptibility reports. Effective ART may reduce the frequency, severity, and recurrence of campylobacter infections.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 9 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bartonellosis	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis: • Doxycycline 100 mg PO or IV q12h **(AII)**, *or* • Erythromycin 500 mg PO or IV q6h **(AII)** CNS Infections: • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h **(AIII)** Confirmed *Bartonella* Endocarditis: • (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) for 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)** Other Severe Infections: • (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) q12h **(BIII)**, *or* • (Erythromycin 500 mg PO or IV q6h) +/- RIF 300 mg PO or IV q12h **(BIII)** Duration of Therapy: • At least 3 months **(AII)**	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, And Osteomyelitis: • Azithromycin 500 mg PO daily **(BIII)** • Clarithromycin 500 mg PO BID **(BIII)** Confirmed *Bartonella* Endocarditis but with Renal Insufficiency: • (Doxycycline 100 mg IV + RIF 300 mg PO or IV) q12h for 2 weeks, then continue with doxycycline 100 mg IV or PI q12h **(BII)**	When RIF is used, take into consideration the potential for significant interaction with ARV drugs and other medications (see Table 5 for dosing recommendations). If relapse occurs after initial (>3 month) course of therapy, long-term suppression with doxycycline or a macrolide is recommended as long as CD4 count <200 cells/μL **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 10 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Syphilis (*Treponema pallidum* Infection)	Early Stage (Primary, Secondary, and Early-Latent Syphilis): • Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** Late-Stage (Tertiary–Cardiovascular or Gummatous Disease): • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** (Note: rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management) Neurosyphilis (Including Otic or Ocular Disease): • Aqueous crystalline penicillin G 18–24 million units per day (administered as 3–4 million units IV q4h or by continuous IV infusion) for 10–14 days **(AII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of IV therapy **(CIII)**	Early Stage (Primary, Secondary, and Early-Latent Syphilis): *For penicillin-allergic patients* • Doxycycline 100 mg PO BID for 14 days **(BII)**, *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days **(BII)**, *or* • Azithromycin 2 g PO for 1 dose **(BII)** (Note: azithromycin is not recommended for men who have sex with men or pregnant women **(AII)**) Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): *For penicillin-allergic patients* • Doxycycline 100 mg PO BID for 28 days **(BIII)** Neurosyphilis: • Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO QID for 10–14 days **(BII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of above **(CIII)**, *or* • *For penicillin-allergic patients:* Desensitization to penicillin is the preferred approach **(BIII)**; if not feasible, ceftriaxone, 2 g IV daily for 10–14 days **(BII)**	The efficacy of non-penicillin alternatives has not been evaluated in HIV-infected patients and they should be used only with close clinical and serologic monitoring. Combination of procaine penicillin and probenecid **is not recommended** for patients who are allergic to sulfa-containing medications **(AIII)**. The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgia that can occur within the first 24 hours after therapy for syphilis. This reaction occurs most frequently in patients with early syphilis, high non-treponemal titers, and prior penicillin treatment.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 11 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Mucocutaneous candidiasis	For Oropharyngeal Candidiasis; Initial Episodes (For 7–14 Days): *Oral Therapy* • Fluconazole 100 mg PO daily **(AI)**, *or* *Topical Therapy* • Clotrimazole troches, 10 mg PO 5 times daily **(BI)**, *or* • Miconazole mucoadhesive buccal 50-mg tablet—apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush) **(BI)** For Esophageal Candidiasis (For 14–21 Days): • Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, *or* • Itraconazole oral solution 200 mg PO daily **(AI)** For Uncomplicated Vulvo-Vaginal Candidiasis: • Oral fluconazole 150 mg for 1 dose **(AII)**, *or* • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)** For Severe or Recurrent Vulvo-Vaginal Candidiasis: • Fluconazole 100–200 mg PO daily for ≥7 days **(AII)**, *or* • Topical antifungal ≥7 days **(AII)**	For Oropharyngeal Candidiasis; Initial Episodes (For 7–14 Days): *Oral Therapy* • Itraconazole oral solution 200 mg PO daily **(BI)**, *or* • Posaconazole oral suspension 400 mg PO BID for 1 day, then 400 mg daily **(BI)** *Topical Therapy* • Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily **(BII)** For Esophageal Candidiasis (For 14–21 Days): • Voriconazole 200 mg PO or IV BID **(BI)**, *or* • Anidulafungin 100 mg IV 1 time, then 50 mg IV daily **(BI)**, *or* • Caspofungin 50 mg IV daily **(BI)**, *or* • Micafungin 150 mg IV daily **(BI)**, *or* • Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**, *or* • Lipid formulation of amphotericin B 3–4 mg/kg IV daily **(BIII)** For Uncomplicated Vulvo-Vaginal Candidiasis: • Itraconazole oral solution 200 mg PO daily for 3–7 days **(BII)**	Chronic or prolonged use of azoles may promote development of resistance. Higher relapse rate for esophageal candidiasis seen with echinocandins than with fluconazole use. Suppressive therapy usually not recommended **(BIII)** unless patients have frequent or severe recurrences. If Decision Is to Use Suppressive Therapy: *Oropharyngeal candidiasis:* • Fluconazole 100 mg PO daily or three times weekly **(BI)**, *or* • Itraconazole oral solution 200 mg PO daily **(CI)** *Esophageal candidiasis:* • Fluconazole 100–200 mg PO daily **(BI)**, *or* • Posaconazole 400 mg PO BID **(BII)** *Vulvo-vaginal candidiasis:* • Fluconazole 150 mg PO once weekly **(CII)**

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 12 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptococcosis	Cryptococcal Meningitis *Induction Therapy (for at least 2 weeks, followed by consolidation therapy):* • Liposomal amphotericin B 3–4 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)** (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) *Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • Fluconazole 400 mg PO (or IV) daily **(AI)** *Maintenance Therapy:* • Fluconazole 200 mg PO daily for at least 12 months **(AI)** For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease: • Treatment same as for cryptococcal meningitis **(BIII)** Non-CNS Cryptococcosis with Mild-to-Moderate Symptoms and Focal Pulmonary Infiltrates: • Fluconazole, 400 mg PO daily for 12 months **(BIII)**	Cryptococcal meningitis *Induction Therapy (for at least 2 weeks, followed by consolidation therapy):* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)**, *or* • Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(BII)**, *or* • Liposomal amphotericin B 3-4 mg/kg IV daily + fluconazole 800 mg PO or IV daily **(BIII)**, *or* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + fluconazole 800 mg PO or IV daily **(BI)**, *or* • Fluconazole 400–800 mg PO or IV daily + flucytosine 25 mg/kg PO QID **(BII)**, *or* • Fluconazole 1200 mg PO or IV daily **(CII)** *Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • Itraconazole 200 mg PO BID for 8 weeks—less effective than fluconazole **(CI)** *Maintenance Therapy:* • No alternative therapy recommendation	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 30–80 mcg/mL) or close monitoring of blood counts for development of cytopenia. Dosage should be adjusted in patients with renal insufficiency **(BII)**. Opening pressure should always be measured when an LP is performed **(AII)**. Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure **(BIII)**. Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**. Corticosteroid should not be routinely used during induction therapy unless it is used for management of IRIS **(AI)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 13 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Histoplasmosis	Moderately Severe to Severe Disseminated Disease *Induction Therapy (for at least 2 weeks or until clinically improved):* • Liposomal amphotericin B 3 mg/kg IV daily **(AI)** *Maintenance Therapy* • Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID **(AII)** Less Severe Disseminated Disease *Induction and Maintenance Therapy:* • Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID **(AII)** *Duration of Therapy:* • At least 12 months Meningitis *Induction Therapy (4–6 weeks):* • Liposomal amphotericin B 5 mg/kg/day **(AIII)** *Maintenance Therapy:* • Itraconazole 200 mg PO BID to TID for ≥1 year and until resolution of abnormal CSF findings **(AII)** Long-Term Suppression Therapy: *For patients with severe disseminated or CNS infection **(AIII)** after completion of at least 12 months of therapy; and those who relapse despite appropriate therapy **(BIII)**:* • Itraconazole 200 mg PO daily **(AIII)**	Moderately Severe to Severe Disseminated Disease *Induction Therapy (for at least 2 weeks or until clinically improved):* • Amphotericin B lipid complex 3 mg/kg IV daily **(AIII)**, *or* • Amphotericin B cholesteryl sulfate complete 3 mg/kg IV daily **(AIII)** Alternatives to Itraconazole for Maintenance Therapy or Treatment of Less Severe Disease: • Voriconazole 400 mg PO BID for 1 day, then 200 mg BID **(BIII)**, *or* • Posaconazole 400 mg PO BID **(BIII)** • Fluconazole 800 mg PO daily **(CII)** Meningitis: • No alternative therapy recommendation Long-Term Suppression Therapy: • Fluconazole 400 mg PO daily **(BIII)**	Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. Refer to Table 5 for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities. Random serum concentration of itraconazole + hydroitraconazole should be >1 µg/mL. Clinical experience with voriconazole or posaconazole in the treatment of histoplasmosis is limited. Acute pulmonary histoplasmosis in HIV-infected patients with CD4 counts >300 cells/µL should be managed as non-immunocompromised host **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 14 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Coccidioidomycosis	Clinically Mild Infections (e.g., Focal Pneumonia): • Fluconazole 400 mg* PO daily **(AII)**, *or* • Itraconazole 200 mg* PO BID **(BII)** Bone or Joint Infections: • Itraconazole 200 mg* PO BID **(AI)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • Lipid formulation amphotericin B 3-5 mg/kg IV daily **(AIII)**, *or* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)** • Duration of therapy: continue until clinical improvement, then switch to a triazole **(BIII)** Meningeal Infections: • Fluconazole 400–800 mg* IV or PO daily **(AII)**	Mild Infections (Focal Pneumonia) *For Patients Who Failed to Respond to Fluconazole or Itraconazole:* • Posaconazole 300mg delayed-release tablet* PO BID x 1 day, then once daily **(BIII)**, *or* • Posaconazole 400 mg oral suspension* PO BID **(BII)**, *or* • Voriconazole 200 mg* PO BID **(BIII)** Bone or Joint Infection: • Fluconazole 400 mg* PO daily **(BI)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • Some specialists will add a triazole (fluconazole* or itraconazole*,) 400 mg per day to amphotericin B therapy and continue triazole once amphotericin B is stopped **(BIII)**. Meningeal Infections: • Itraconazole 200 mg* PO TID for 3 days, then 200 mg PO BID **(BII)**, *or* • Voriconazole 200–400 mg* PO BID **(BIII)**, *or* • Posaconazole 300 mg delayed-release tablet* PO BID x 1 day, then once daily **(CIII)**, *or* • Posaconazole 400 mg oral suspension* PO BID **(CIII)**, *or* • Intrathecal amphotericin B deoxycholate, when triazole antifungals are ineffective **(AIII)**	Relapse can occur in 25%–33% of HIV-negative patients with diffuse pulmonary or disseminated diseases. Therapy should be given for at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts **(BIII)**. Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of HIV-infected patients after discontinuation of triazole therapy **(AII)**. *Fluconazole, itraconazole, posaconazole, and voriconazole may have significant interactions with other medications including ARV drugs. These interactions are complex and can be bi-directional. Refer to Table 5 or Antiretroviral guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities. Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 15 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cytomegalovirus (CMV) Disease	CMV Retinitis *Induction Therapy (followed by Chronic Maintenance Therapy)*: *For Immediate Sight-Threatening Lesions (within 1500 microns of the fovea):* • Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) for 1-4 doses over a period of 7-10 days to achieve high intraocular concentration faster **(AIII)**; plus • Valganciclovir 900 mg PO BID for 14–21 days, then 900mg once daily **(AI)**: *For Peripheral Lesions:* • Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily **(AI)** Chronic Maintenance: • Valganciclovir 900 mg PO daily **(AI)** for 3-6 months until ART induced immune recovery (see Table 4) CMV Esophagitis or Colitis: • Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can tolerate oral therapy **(BI)** • Duration: 21–42 days or until symptoms have resolved **(CII)** • Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)**. Well-Documented, Histologically Confirmed CMV Pneumonia: • Experience for treating CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis) **(CIII)**. • The optimal duration of therapy and the role of oral valganciclovir have not been established. CMV Neurological Disease ***Note: Treatment should be initiated promptly.*** • Ganciclovir 5 mg/kg IV q12h + (foscarnet 90 mg/kg IV q12h or 60 mg/kg IV q8h) to stabilize disease and maximize response, continue until symptomatic improvement and resolution of neurologic symptoms **(CIII)**	CMV Retinitis *For Immediate Sight-Threatening Lesions (within 1500 microns of the fovea): Intravitreal therapy as listed in the Preferred section, plus one of the following:* *Alternative Systemic Induction Therapy (followed by Chronic Maintenance Therapy):* • Ganciclovir 5 mg/kg IV q12h for 14–21 days **(AI)**, *or* • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h for 14–21 days **(AI)**, *or* • Cidofovir 5 mg/kg/week IV for 2 weeks; saline hydration before and after therapy and probenecid, 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after the dose (total of 4 g) **(BI)**. (Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid.) *Chronic Maintenance (for 3-6 months until ART induced immune recovery (see Table 4):* • Ganciclovir 5 mg/kg IV 5–7 times weekly **(AI)**, *or* • Foscarnet 90–120 mg/kg IV once daily **(AI)**, *or* • Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above **(BI)** CMV Esophagitis or Colitis: • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h **(BI)** for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, *or* • Valganciclovir 900 mg PO q12h in milder disease and if able to tolerate PO therapy **(BII)**, *or* • Duration: 21–42 days or until symptoms have resolved **(CII)** • For mild disease, if ART can be initiated without delay, consider withholding CMV therapy **(CIII)**.	The choice of therapy for CMV retinitis should be individualized, based on location and severity of the lesions, level of immunosuppression, and other factors (e.g., concomitant medications and ability to adhere to treatment) **(AIII)**. Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reduce CMV visceral disease and improve survival. Whenever feasible, treatment should include systemic therapy. The ganciclovir ocular implant, which is effective for treatment of CMV retinitis is no longer available. For sight threatening retinitis, intravitreal injections of ganciclovir or foscarnet can be given to achieve higher ocular concentration faster. Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution **(AIII)**. IRU may develop in the setting of immune reconstitution. Treatment of IRU • Periocular corticosteroid or short courses of systemic steroid **(BIII)**. Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART **(BIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 16 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cytomegalovirus (CMV) Disease, continued	• The optimal duration of therapy and the role of oral valganciclovir have not been established. • Optimize ART to achieve viral suppression and immune reconstitution **(BIII)**.		
Herpes Simplex Virus (HSV) Disease	Orolabial Lesions (For 5–10 Days): • Valacyclovir 1 g PO BID **(AIII)**, *or* • Famciclovir 500 mg PO BID **(AIII)**, *or* • Acyclovir 400 mg PO TID **(AIII)** Initial or Recurrent Genital HSV (For 5–14 Days): • Valacyclovir 1 g PO BID **(AI)**, *or* • Famciclovir 500 mg PO BID **(AI)**, *or* • Acyclovir 400 mg PO TID **(AI)** Severe Mucocutaneous HSV: • Initial therapy acyclovir 5 mg/kg IV q8h **(AIII)** • After lesions begin to regress, change to PO therapy as above. Continue until lesions are completely healed. Chronic Suppressive Therapy *For patients with severe recurrences of genital herpes **(AI)** or patients who want to minimize frequency of recurrences **(AI)**:* • Valacyclovir 500 mg PO BID **(AI)** • Famciclovir 500 mg PO BID **(AI)** • Acyclovir 400 mg PO BID **(AI)** • Continue indefinitely regardless of CD4 cell count.	For Acyclovir-Resistant HSV *Preferred Therapy:* • Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)** *Alternative Therapy **(CIII)**:* • IV cidofovir (dosage as in CMV retinitis), *or* • Topical trifluridine, *or* • Topical cidofovir, *or* • Topical imiquimod Duration of Therapy: • 21–28 days or longer	Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. Topical formulations of trifluridine and cidofovir are not commercially available. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 17 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Varicella Zoster Virus (VZV) Disease	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (For 5–7 Days):* • Valacyclovir 1 g PO TID **(AII)**, *or* • Famciclovir 500 mg PO TID **(AII)** *Severe or Complicated Cases:* • Acyclovir 10–15 mg/kg IV q8h for 7–10 days **(AIII)** • May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement **(BIII)**. Herpes Zoster (Shingles) *Acute Localized Dermatomal:* • For 7–10 days; consider longer duration if lesions are slow to resolve • Valacyclovir 1 g PO TID **(AII)**, *or* • Famciclovir 500 mg TID **(AII)** *Extensive Cutaneous Lesion or Visceral Involvement:* • Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident **(AII)** • May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV), to complete a 10–14 day course **(BIII)**. Progressive Outer Retinal Necrosis (PORN): • (Ganciclovir 5 mg/kg +/- foscarnet 90 mg/kg) IV q12h + (ganciclovir 2 mg/0.05mL +/- foscarnet 1.2 mg/0.05 ml) intravitreal injection BIW **(AIII)** • Initiate or optimize ART **(AIII)** Acute Retinal Necrosis (ARN): • (Acyclovir 10-15 mg/kg IV q8h) + (ganciclovir 2 mg/0.05mL intravitreal injection BIW X 1-2 doses) for 10-14 days, followed by valacyclovir 1g PO TID for 6 weeks **(AIII)**	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (For 5-7 Days):* • Acyclovir 800 mg PO 5 times/day **(BII)** Herpes Zoster (Shingles) *Acute Localized Dermatomal:* • For 7–10 days; consider longer duration if lesions are slow to resolve • Acyclovir 800 mg PO 5 times/day **(BII)**	In managing VZV retinitis - Consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended **(AIII)**. Duration of therapy for VZV retinitis is not well defined, and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses. Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 18 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
HHV-8 Diseases *(Kaposi Sarcoma [KS], Primary Effusion Lymphoma [PEL], Multicentric Castleman's Disease [MCD])*	Mild To Moderate KS (ACTG Stage T0): • Initiate or optimize ART **(AII)** Advanced KS [ACTG Stage T1, Including Disseminated Cutaneous **(AI)** Or Visceral KS **(BIII)**]: • Chemotherapy (per oncology consult) + ART Primary Effusion Lymphoma: • Chemotherapy (per oncology consult) + ART **(AI)** • PO valganciclovir or IV ganciclovir can be used as adjunctive therapy **(CIII)**. MCD: • Valganciclovir 900 mg PO BID for 3 weeks **(CII)**, *or* • Ganciclovir 5 mg/kg IV q12h for 3 weeks **(CII)**, *or* • Valganciclovir 900 mg PO BID + zidovudine 600 mg PO q6h for 7–21 days **(CII)**	MCD • Rituximab (375 mg/m^2 given weekly for 4–8 weeks) may be an alternative to or used adjunctively with antiviral therapy **(CII)**.	• Patients who received rituximab for MCD may experience subsequent exacerbation or emergence of KS
Human Papillomavirus (HPV) Disease	**Treatment of Condyloma Acuminata (Genital Warts)** Patient-Applied Therapy for Uncomplicated External Warts That Can Be Easily Identified by Patients: • Podophyllotoxin (e.g., podofilox 0.5% solution or 0.5% gel): Apply to all lesions BID for 3 consecutive days, followed by 4 days of no therapy, repeat weekly for up to 4 cycles, until lesions are no longer visible **(BIII)**, *or* • Imiquimod 5% cream: Apply to lesion at bedtime and remove in the morning on 3 non-consecutive nights weekly for up to 16 weeks, until lesions are no longer visible. Each treatment should be washed with soap and water 6–10 hours after application **(BII)**, *or* • Sinecatechins 15% ointment: Apply to affected areas TID for up to 16 weeks, until warts are completely cleared and not visible **(BIII)**.	Provider-Applied Therapy for Complex or Multicentric Lesions, or Lesions Inaccessible to Patient *Applied Therapy:* • Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen. Repeat every 1–2 weeks for up to 4 weeks, until lesions are no longer visible **(BIII)**. Some providers allow the lesion to thaw, then freeze a second time in each session **(BIII)**, *or* • Trichloroacetic acid or bichloroacetic acid cauterization: 80%–90% aqueous solution, apply to wart only, allow to dry until a white frost develops. Repeat weekly for up to 6 weeks, until lesions are no longer visible **(BIII)**, *or* • Surgical excision **(BIII)** or laser surgery **(CIII)** to external or anal warts, *or* • Podophyllin resin 10%–25% in tincture of benzoin: Apply to all lesions (up to 10 cm^2), then wash off a few hours later, repeat weekly for up to 6 weeks until lesions are no longer visible **(CIII)**.	HIV-infected patients may have larger or more numerous warts and may not respond as well to therapy for genital warts when compared to HIV-uninfected individuals. Topical cidofovir has activity against genital warts, but the product is not commercially available **(CIII)**. Intralesional interferon-alpha is usually not recommended because of high cost, difficult administration, and potential for systemic side effects **(CIII)**. The rate of recurrence of genital warts is high despite treatment in HIV-infected patients. There is no consensus on the treatment of oral warts. Many treatments for anogenital warts cannot be used in the oral mucosa. Surgery is the most common treatment for oral warts that interfere with function or for aesthetic reasons.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 19 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Hepatitis B Virus (HBV) Disease	ART is recommended for all HIV/HBV-co-infected patients regardless of CD4 cell count **(AII)**. ART regimen should include 2 drugs that are active against both HBV and HIV, such as [tenofovir 300 mg + emtricitabine 200 mg (or lamivudine 300 mg)] PO once daily (+ additional drug(s) for HIV) **(AIII)**. Duration: Continue treatment indefinitely **(CIII)**	For Patients Who Refuse or Are Unable to Take ART or Who Are HIV Long-Term Non-Progressors: • HBV treatment is indicated for patients with elevated ALT and HBV DNA >2,000 IU/mL significant liver fibrosis, advanced liver disease or cirrhosis **(AI)**. • Peginterferon alfa-2a 180 µg SQ once weekly for 48 weeks **(CIII)**, *or* • Peginterferon alfa 2b 1.5 µg/kg SQ once weekly for 48 weeks **(CIII)**. If Tenofovir Cannot Be Used as Part of HIV/HBV Therapy (Because of Current or High Risk of Renal Dysfunction): • Use a fully suppressive ART regimen without tenofovir, and with the addition of entecavir (dose adjustment according to renal function) **(BIII)**.	Directly acting HBV drugs such as adefovir, emtricitabine, entecavir, lamivudine, telbivudine, or tenofovir **must not be given** in the absence of a fully suppressive ART regimen to avoid selection of drug resistance HIV **(AI)**. Cross-resistance to emtricitabine or telbivudine should be assumed in patients with suspected or proven lamivudine-resistance. When changing ART regimens, continue agents with anti-HBV activity **(BIII)**. If anti-HBV therapy is discontinued and a flare occurs, therapy should be re-instituted because it can be potentially life-saving **(AIII)**.
Hepatitis C Virus (HCV) Disease	The field of HCV drug development is evolving rapidly. The armamenarium of approved drugs is likely to expand considerably in the next few years. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most updated recommendations.		
Progressive Multifocal Leukoencephalopathy (PML) (JC Virus Infections)	There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV. Initiate ART immediately in ART-naive patients **(AII)**. Optimize ART in patients who develop PML in phase of HIV viremia on ART **(AIII)**	None.	Corticosteroids may be used for PML-IRIS characterized by contrast enhancement, edema or mass effect, and with clinical deterioration **(BIII)** (see text for further discussion).

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 20 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Malaria	Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infection should be hospitalized for evaluation, initiation of treatment, and observation **(AIII)**. Treatment recommendations for HIV-infected patients are the same as HIV-uninfected patients **(AIII)**. Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, region of infection, and the likely drug susceptibility of the infected species, and can be found at http://www.cdc.gov/malaria.	When suspicion for malaria is low, antimalarial treatment should not be initiated until the diagnosis is confirmed.	For treatment recommendations for specific regions, clinicians should refer to the following web link: http://www.cdc.gov/malaria/ or call the CDC Malaria Hotline: (770) 488-7788: M–F 8 AM–4:30 PM ET, or (770) 488-7100 after hours
Leishmaniasis, visceral	For Initial Infection: • Liposomal amphotericin B 2–4 mg/kg IV daily **(AII)**, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) **(AII)** • To achieve total dose of 20–60 mg/kg **(AII)** Chronic Maintenance Therapy (Secondary Prophylaxis); Especially in Patients with CD4 Count <200 cells/μL: • Liposomal amphotericin B 4 mg/kg every 2–4 weeks **(AII)**, *or* Amphotericin B lipid complex **(AII)** 3 mg/kg every 21 days **(AII)**	For Initial Infection: • Other lipid formulation of amphotericin B, dose and schedule as in Preferred Therapy, *or* • Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g **(BII)**, *or* • Sodium stibogluconate (pentavalent antimony) **(BII)** 20 mg/kg IV or IM daily for 28 days. *Another Option:* • Miltefosine 100 mg PO daily for 4 weeks (available in the United States under a treatment IND) **(CIII)** Chronic Maintenance Therapy (Secondary Prophylaxis): Sodium stibogluconate 20 mg/kg IV or IM every 4 weeks **(BII)**	ART should be initiated or optimized **(AIII)**. For sodium stibogluconate, contact the CDC Drug Service at (404) 639-3670 or drugservice@cdc.gov.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 21 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Leishmaniasis, cutaneous	• Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days **(BIII)**, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII)**, *or* • Sodium stibogluconate 20 mg/kg IV or IM daily for 3–4 weeks **(BIII)** Chronic Maintenance Therapy: May be indicated in immunocompromised patients with multiple relapses **(CIII)**	Possible Options Include: • Oral miltefosine (can be obtained via a treatment IND), *or* • Topical paromomycin, *or* • Intralesional sodium stibogluconate, *or* • Local heat therapy No data exist for any of these agents in HIV-infected patients; choice and efficacy dependent on species of *Leishmania*.	None.
Chagas Disease (American Trypanosomiasis)	For Acute, Early Chronic, and Re-Activated Disease: • Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days **(BIII)** (not commercially available in the United States; contact the CDC Drug Service at drugservice@cdc.gov or (404) 639-3670, or the CDC emergency operations center at (770) 488-7100)	For Acute, Early Chronic, And Reactivated Disease Nifurtimox 8–10 mg/kg/day PO for 90–120 days **(CIII)** (not commercially available in the U.S., contact the CDC Drug Service at drugservice@cdc.gov or (404) 639-3670, or the CDC emergency operations center at (770) 488-7100)	Treatment is effective in reducing parasitemia and preventing clinical symptoms or slowing disease progression. It is ineffective in achieving parasitological cure. Duration of therapy has not been studied in HIV-infected patients. Initiate or optimize ART in patients undergoing treatment for Chagas disease, once they are clinically stable **(AIII)**.
Penicilliosis marneffei	For Acute Infection in Severely Ill Patients: • Liposomal amphotericin B 3–5 mg/kg/day IV for 2 weeks, followed by itraconazole 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy (as below) For Mild Disease: • Itraconazole 200 mg PO BID for 8 weeks **(BII)**; followed by chronic maintenance therapy (as below) Chronic Maintenance Therapy (Secondary Prophylaxis): • Itraconazole 200 mg PO daily **(AI)**	For Acute Infection in Severely Ill Patients: • Voriconazole 6 mg/kg IV q12h for 1 day, then 4 mg/kg IV q12h for at least 3 days, followed by 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by maintenance therapy For Mild Disease: • Voriconazole 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy	ART should be initiated simultaneously with treatment for penicilliosis to improve treatment outcome **(CIII)**. Itraconazole and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. Refer to Table 5 for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 22 of 22)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Isosporiasis	For Acute Infection: • TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days **(AII)**, *or* • TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days **(BI)** • Can start with BID dosing first and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist **(BIII)** • IV therapy may be used for patients with potential or documented mal-absorption. Chronic Maintenance Therapy (Secondary Prophylaxis): • In patients with CD4 count <200/µL, TMP-SMX (160 mg/800 mg) PO TIW **(AI)**	For Acute Infection: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily **(BIII)**, *or* • Ciprofloxacin 500 mg PO BID for 7 days **(CI)** as a second line alternative Chronic Maintenance Therapy (Secondary Prophylaxis): • TMP-SMX (160 mg/800 mg) PO daily or (320 mg/1600 mg) TIW **(BIII)** • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)** • Ciprofloxacin 500 mg TIW **(CI)** as a second-line alternative	Fluid and electrolyte management in patients with dehydration **(AIII)**. Nutritional supplementation for malnourished patients **(AIII)**. Immune reconstitution with ART may result in fewer relapses **(AIII)**.

Key to Acronyms: ACTG = AIDS Clinical Trials Group; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = ritonavir-boosted atazanavir; BID = twice a day; BIW = twice weekly; BOC = boceprevir; CD4 = CD4 T lymphocyte cell; CDC = The Centers for Disease Control and Prevention; CFU = colony-forming unit; CNS = central nervous system; CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; ddI = didanosine; DOT = directly-observed therapy; DS = double strength; EFV = efavirenz; EMB = ethambutol; g = gram; G6PD = Glucose-6-phosphate dehydrogenase; GI = gastrointestinal; ICP = intracranial pressure; ICU = intensive care unit; IM = intramuscular; IND = investigational new drug; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LP = lumbar puncture; mg = milligram; mmHg = millimeters of mercury; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NSAID = non-steroidal anti-inflammatory drugs; PegIFN = Pegylated interferon; PI = protease inhibitor; PO = oral; PORN = Progressive Outer Retinal Necrosis; PZA = pyrazinamide; qAM = every morning; QID = four times a day; q(n)h = every "n" hours; qPM = every evening; RBV = ribavirin; RFB = rifabutin; RIF = rifampin; SQ = subcutaneous; SS = single strength; TID = three times daily; TVR = telaprevir; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Evidence Rating:

Strength of Recommendation:

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III: Expert opinion

In cases where there are no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected patients exist that can plausibly guide management decisions for patients with HIV/AIDS, the data will be rated as III but will be assigned recommendations of A, B, C depending on the strength of recommendation.

Table 3. Recommended Doses of First-Line Drugs for Treatment of Tuberculosis in Adults and Adolescents (Last updated May 18, 2017; last reviewed May 18, 2017)

Drug	Daily
Isoniazid	5 mg/kg (usual dose 300 mg)
Rifampin[a] **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/COBI, or TAF	10 mg/kg (usual dose 600 mg)
Rifabutin[a]	5 mg/kg (usual dose 300 mg)
without HIV PIs, EFV, RPV	
with HIV PIs	150 mg[b]
with EFV	450–600 mg
with TAF or EVG/COBI containing regimens	not recommended
Pyrazinamide (weight-based dosing)	1000 mg (18.2–25.0 mg/kg)
40–55 kg	
56–75 kg	1500 mg (20.0–26.8 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)
>90 kg	2000 mg[c]
Ethambutol	800 mg (14.5–20.0 mg/kg)
40–55 kg	
56–75 kg	1200 mg (16.0–21.4 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)
>90 kg	1600 mg[c]

[a] For more detailed guidelines on use of different antiretroviral drugs with rifamycin, clinicians should refer to the Drug Interactions section of the Adult and Adolescent ARV Guidelines

[b] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

[c] Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 1 of 3) (Last updated November 10, 2016; last reviewed November 10, 2016)

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/ Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
***Pneumocystis* Pneumonia**	CD4 count increased from <200 to >200 cells/μL for >3 months in response to ART **(AI)**	CD4 count <200 cells/mm^3 **(AIII)**	CD4 count increased from <200 cells/μL to >200 cells/μL for >3 months in response to ART **(BII)** If PCP was diagnosed when CD4 count was >200 cells/μL, continue prophylaxis for life regardless of CD4 count rise in response to ART **(BIII)**.	• CD4 count <200 cells/μL **(AIII)**, *or* • If PCP recurred at CD4 count >200 cells/μL, prophylaxis should be continued for life **(CIII)**.
***Toxoplasma gondii* Encephalitis**	CD4 count increased to >200 cells/μL for >3 months in response to ART **(AI)**	CD4 count <100 to 200 cells/μL **(AIII)**	Successfully completed initial therapy, remain free of signs and symptoms of TE, and CD4 count >200 cells/μL for >6 months in response to ART **(BI)**.	CD4 count <200 cells/μL **(AIII)**
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular **(BIII)** or ocular **(CIII)** microsporidiosis and CD4 count >200 cells/μL for >6 months in response to ART.	No recommendation
Disseminated *Mycobacterium avium* Complex Disease	CD4 count >100 cells/μL for ≥3 months in response to ART **(AI)**	CD4 count <50 cells/μL **(AIII)**	If the following criteria are fulfilled **(AI)**: • Completed ≥12 months of therapy, *and* • No signs and symptoms of MAC disease, *and* • Have sustained (>6 months) CD4 count >100 cells/μL in response to ART.	CD4 count <100 cells/μL **(AIII)**
Salmonellosis	Not applicable	Not applicable	Resolution of *Salmonella* infection and after response to ART with sustained viral suppression and CD4 counts >200 cells/μL **(CII)**	No recommendation
Bartonellosis	Not applicable	Not applicable	• Received at least 3–4 months of treatment, *and* • CD4 count >200 cells/μL for ≥6 months **(CIII)** • Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by four-fold **(CIII)**.	No recommendation
Mucosal Candidiasis	Not applicable	Not applicable	If used, reasonable to discontinue when CD4 count >200 cells/μL **(AIII)**.	No recommendation

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 2 of 3)

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/ Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
Cryptococcal Meningitis	Not applicable	Not applicable	If the following criteria are fulfilled **(BII)**: • Completed initial (induction and consolidation) therapy, *and* • Received at least 1 year of maintenance therapy, *and* • Remain asymptomatic of cryptococcal infection, *and* • CD4 count ≥100 cells/μL for >3 months, and with suppressed plasma HIV RNA in response to ART	CD4 count <100 cells/μL **(AIII)**
***Histoplasma capsulatum* Infection**	CD4 count >150 cells/μL for 6 months while on ART **(BIII)**	For patients at high risk of acquiring histoplasmosis, restart at CD4 count <150 cells/μL **(CIII)**	If the following criteria **(AI)** are fulfilled: • Received itraconazole for >1 year, *and* • Negative fungal blood cultures, *and* • CD4 count ≥150 cells/μL for ≥6 months in response to ART, *and* • Serum *Histoplasma* antigen <2 ng/mL	CD4 count <150 cells/mm^3 **(BIII)**
Coccidioido-mycosis	CD4 count ≥250 cells/μL and with viral suppression while on ART **(CIII)**	Restart at CD4 count <250 cells/μL **(BIII)**	Only for patients with focal coccidioidal pneumonia **(AII)**: • Clinically responded to ≥ 6 months antifungal therapy, with CD4 count ≥250 cells/mm^3, and with viral suppression while on ART. • Should continue monitoring for recurrence with serial chest radiographs and coccidioidal serology every 6-12 months. For patients with diffuse pulmonary **(BIII)**, disseminated non-meningeal **(BIII)**: • Therapy is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts For meningeal diseases **(AII)**: Suppressive therapy should be continued indefinitely, even with increase in CD4 count on ART.	No recommendation

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 3 of 3)

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/ Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
Cytomegalovirus Retinitis	Not applicable	Not applicable	• CMV treatment for at least 3 to 6 months; and with CD4 count >100 cells/μL for >3 to 6 months in response to ART **(AII)**. • Therapy should be discontinued only after consultation with an ophthalmologist, taking into account anatomic location of lesions, vision in the contralateral eye, and feasibility of regular ophthalmologic monitoring. • Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping therapy for early detection of relapse or immune restoration uveitis, and then periodically after sustained immune reconstitution **(AIII)**.	CD4 count <100 cells/μL **(AIII)**
***Penicillium marneffei* Infection**	CD4 count >100 cells/μL for >6 months in response to ART **(BII)**	CD4 count <100 cells/μL **(BIII)**	CD4 count >100 cells/μL for ≥6 months in response to ART **(BII)**	• CD4 count <100 cells/μL (AIII), *or* • If penicilliosis recurs at CD4 count >100 cells/μL **(CIII)**
Visceral Leishmaniasis (and possibly cutaneous leishmaniasis in immunocompromised patients with multiple relapses)	Not applicable	Not applicable	There is no consensus regarding when to stop secondary prophylaxis. Some investigators suggest that therapy can be stopped if CD4 count increases to >200 to 350 cells/μL for 3–6 months in response to ART, but others suggest that therapy should be continued indefinitely.	No recommendation
***Isospora belli* Infection**	Not applicable	Not applicable	Sustained increase in CD4 count to >200 cells/μL for >6 months in response to ART and without evidence of *I. belli* infection **(BIII)**	No recommendation

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; TE = *Toxoplasma* encephalitis

Evidence Rating:

Strength of Recommendation:

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III: Expert opinion

In cases where there are no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected patients exist that can plausibly guide management decisions for patients with HIV/AIDS, the data will be rated as III but will be assigned recommendations of A, B, C depending on the strength of recommendation.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 1 of 15) (Last updated March 13, 2017; last reviewed March 13, 2017)

This table lists the known or suspected/predicted pharmacokinetic interactions between drugs used for the treatment or prevention of HIV-associated opportunistic infections (OIs). Many of the drugs listed in this table may also interact with antiretroviral drugs. Clinicians should refer to the drug interaction tables in the most current Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents to assess interaction potentials between OI drugs and antiretroviral therapy (ART).

Throughout the table, three recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The rationale for these recommendations are summarized below:

"Do not co-administer"

Indicates there is either strong evidence or strong likelihood that the drug-drug interaction cannot be managed with a dose modification of one or both drugs, and will/may result in either:

1) Increase in concentrations of one or both drugs, which may lead to excessive risk of toxicity; *or*
2) Decrease in concentrations of one or both drugs, which may render one or both drugs ineffective.

"Co-administration should be avoided, if possible"

There is a potential for significant pharmacokinetic interactions. However, co-administration of the drugs may be necessary if there are no other acceptable therapeutic options that provide a more favorable benefit-to-risk ratio. If other more favorable options exist, clinicians are advised to consider changing components of the regimen to accommodate a safer or more effective regimen.

"Use with caution"

Drug combinations are recommended to be used with caution when:

1. Pharmacokinetic studies have shown a moderate degree of interaction of unknown clinical significance; *or*
2. Based on the known metabolic pathway of the two drugs, there is a potential for pharmacokinetic interaction of unknown clinical significance.

Rifamycin-Related Interactions

Rifamycins are potent inducers of Phase I and Phase II drug metabolizing reactions. Daily doses of rifampin are well studied, and induction increases over a week or more. Based on limited data, larger doses of rifampin (e.g., 1200 mg) appear to produce the same maximum induction, but more rapidly. Single doses of rifampin may not produce significant induction. In general, rifabutin is about 40% as potent a CYP3A4 inducer as rifampin, but this can vary by substrate and enzymatic reaction. In general, daily rifapentine (for active tuberculosis [TB] disease) is at least as potent an inducer as rifampin. However, the potential of drug interactions with once weekly rifapentine (prescribed with isoniazid for latent TB infection) is not well studied, but may result in reduction of exposure of drugs that are CYP3A4 substrates. When a rifamycin is used with a potential interacting drug, close monitoring for clinical efficacy of the other agent is advised.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 2 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether/ Lumefantrine	Clarithromycin	↑ Lumefantrine expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Artemether and lumefantrine possible	Use with caution. Monitor for artemether- and lumefantrine-associated toxicities.
	Erythromycin	↑ Lumefantrine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Lumefantrine possible	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.
	Rifampin[a]	↓ Artemether, DHA, and lumefantrine AUC by 89%, 85%, and 68%, respectively	Do not co-administer.
	Rifapentine[a]	↓ Artemether, DHA, and lumefantrine expected	Do not co-administer.
	Voriconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
Atovaquone	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↔ Atovaquone (based on data from atovaquone and atazanavir/ritonavir interaction)	No dosage adjustment necessary.
	Doxycycline	Atovaquone conc. ↓ by approximately 40% with tetracycline. No interaction study with doxycycline.	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	Atovaquone C_{SS}↓ 34%; rifabutin C_{SS}↓ 19%	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifampin[a]	Atovaquone C_{SS} ↓ 52%; rifampin C_{SS}↑ 37%	Do not co-administer.
	Rifapentine[a]	↓ Atovaquone expected	Do not co-administer.
Bedaquiline	Clarithromycin	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider alternative HCV regimen.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 3 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Erythromycin	↑ Bedaquiline possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Bedaquiline possible	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Itraconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Posaconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Bedaquiline possible	If co-administered, monitor for bedaquiline efficacy.
	Rifampin[a]	Bedaquiline AUC ↓ 53%	Do not co-administer.
	Rifapentine[a]	Bedaquiline AUC ↓ 55% (with daily rifapentine)	Do not co-administer.
	Voriconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
Caspofungin	Rifabutin[a]	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Rifampin[a]	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
	Rifapentine[a]	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
Chloroquine	Clarithromycin	↑ Chloroquine expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Chloroquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Chloroquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Rifampin[a]	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Rifapentine[a]	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Voriconazole	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
Clarithromycin	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided if possible. Consider azithromycin in place of clarithromycin.
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 4 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	↓ Daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Clarithromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Elbasvir/ Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity. Consider azithromycin in place of clarithromycin.
	Fluconazole	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Itraconazole	↑ Itraconazole and clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If co-administered, monitor for toxicities of both itraconazole and clarithromycin (e.g., QT prolongation), consider monitoring itraconazole conc. and adjust dose accordingly.
	Mefloquine	↑ Mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for mefloquine toxicity (e.g., QT prolongation).
	Posaconazole	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Quinine	↑ Quinine expected; ↑ clarithromycin possible	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Rifabutin[a]	Clarithromycin AUC ↓ by 44%; 14-OH AUC ↑ 57%; rifabutin AUC ↑ 76% to 99%; des-Rbt AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, consider reducing rifabutin dose, monitoring clarithromycin and rifabutin concentrations, and monitoring for rifabutin-associated toxicities (e.g., uveitis).
	Rifampin[a]	Mean clarithromycin conc. ↓ 87%; rifampin AUC ↑ 60%	Do not co-administer. Use azithromycin in place of clarithromycin.
	Rifapentine[a]	↓ Clarithromycin expected; ↑ 14-OH and rifapentine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for rifapentine-associated toxicities, consider monitoring clarithromycin and rifapentine concentrations and adjusting doses accordingly.
	Simeprevir	↑ Simeprevir expected	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Voriconazole	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
Daclatasvir	Clarithromycin	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Erythromycin	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Fluconazole	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Itraconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Posaconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 5 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifabutin[a]	↓ Daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitor for therapeutic efficacy.
	Rifampin[a]	Daclatasvir AUC ↓ 79%	Do not co-administer.
	Rifapentine[a]	↓ Daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitor for therapeutic efficacy.
	Simeprevir	Simeprevir AUC ↑ 44%; daclatasvir AUC ↑ 96%	No dosage adjustment. Monitor for simeprevir and daclatasvir-associated toxicities.
	Voriconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
Dapsone	Rifabutin[a]	Dapsone AUC ↓ 27% to 40%	Co-administration should be avoided if possible. Consider alternatives for dapsone.
	Rifampin[a]	Dapsone conc. ↓ 7- to 10-fold and $t_{1/2}$ ↓ from 24 to 11 hours	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Rifapentine[a]	↓ Dapsone expected	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
Dasabuvir Ombitasvir Paritaprevir Ritonavir	Artemether/ Lumefantrine	↑ Artemether and lumefantrine possible	Use with caution. Monitor for artemether- and lumefantrine-associated toxicities.
	Atovaquone	↔ Atovaquone (based on data from atovaquone and ritonavir/ atazanavir interaction)	No dosage adjustment necessary.
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider alternative HCV regimen.
	Clarithromycin	↑ Clarithromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Erythromycin expected and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Itraconazole	↑ Itraconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole levels. Monitor for itraconazole and HCV regimen-associated toxicities.
	Posaconazole	↑ Posaconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole and HCV regimen-associated toxicities. Monitor posaconazole conc. and adjust dose if necessary.
	Rifabutin[a]	↑ Rifabutin expected; ↓ paritaprevir possible	Co-administration should be avoided if possible. With co-administration, decrease rifabutin dose to 150 mg/ day and monitor rifabutin conc. Monitor HCV regimen for efficacy.
	Rifampin[a]	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Rifapentine[a]	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Voriconazole	Voriconazole AUC ↓ 39% (with ritonavir); ↑ paritaprevir expected	Co-administer only if the benefits outweigh the risk. Monitor voriconazole conc. to guide dosage adjustments.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 6 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Doxycycline	Atovaquone	Atovaquone concentration ↓ by approximately 40% with tetracycline. No interaction study with doxycycline.	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifampin[a]	Doxycycline AUC ↓ by 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifapentine[a]	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
Elbasvir/ Grazoprevir	Clarithromycin	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity. Consider azithromycin in place of clarithromycin.
	Itraconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Posaconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Rifabutin[a]	↓ Elbasvir and grazoprevir possible	Co-administration should be avoided if possible. Consider alternative HCV regimen.
	Rifampin[a]	Grazoprevir AUC ↓ 7%, C_{24} ↓ 90%; ↓ elbasvir expected	Do not co-administer.
	Rifapentine[a]	↓ Elbasvir and grazoprevir possible	Do not co-administer.
	Voriconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided if possible. If co-administered, monitor closely for hepatotoxicity.
Erythromycin	Artemether/ Lumefantrine	↑ Lumefantrine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Bedaquiline	↑ Bedaquiline possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Chloroquine	↑ Chloroquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Daclatasvir	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Erythromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Itraconazole	Itraconazole AUC ↑ 36%; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Posaconazole	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 7 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Quinine	↑ Quinine expected; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ Erythromycin possible; ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy or rifabutin toxicities (e.g., uveitis).
	Rifampin[a]	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Rifapentine[a]	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Simeprevir	Simeprevir AUC ↑ 647%, C_{min} ↑ 1,174%; erythromycin AUC ↑ 90%, C_{min} ↑ 208%	Do not co-administer. Consider azithromycin in place of erythromycin.
	Voriconazole	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
Fluconazole	Artemether/ Lumefantrine	↑ Lumefantrine possible	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline possible	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Daclatasvir	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Erythromycin	↑ Erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ fluconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine and fluconazole toxicity (e.g., QT prolongation).
	Rifabutin[a]	Rifabutin AUC ↑ 80%; ↔ fluconazole	Use with caution. Monitor for rifabutin-associated toxicities (e.g., uveitis). Consider monitoring rifabutin conc.; may need to lower rifabutin dose to 150 mg/day.
	Rifampin[a]	Fluconazole AUC ↓ 23% to 56%	Monitor for antifungal efficacy; may need to raise fluconazole dose.
	Rifapentine[a]	↓ Fluconazole expected	Monitor for antifungal efficacy; may need to raise fluconazole dose.
	Simeprevir	↑ Simeprevir possible	Do not co-administer.
Itraconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 8 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Itraconazole and clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If co-administered, monitor for toxicities of both itraconazole and clarithromycin (e.g., QT prolongation), consider monitoring itraconazole conc. and adjusting dose accordingly.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Itraconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole levels. Monitor for itraconazole and HCV regimen-associated toxicities.
	Elbasvir/ Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	Itraconazole AUC ↑ 36%; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ itraconazole possible	Co-administration should be avoided, if possible. If used concomitantly, monitor for quinine and itraconazole toxicity (e.g, QT prolongation), monitor itraconazole conc. and adjust dose accordingly.
	Rifabutin[a]	Itraconazole AUC ↓ 70%; ↑ rifabutin expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifampin[a]	Itraconazole AUC ↓ 64% to 88%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	↓ Itraconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Simeprevir	↑ Simeprevir expected	Do not co-administer.
Ledipasvir/ Sofosbuvir	Rifabutin[a]	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Ledipasvir AUC ↓ 59%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Simeprevir	Ledipasvir AUC ↑ 92%; simeprevir AUC ↑ 116%	Do not co-administer.
	TAF	Ledipasvir AUC ↑ 79%	No dosage adjustment.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 9 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	TDF	TDF AUC ↑ 98% (when given with EFV/FTC) TDF AUC ↑ 40% (when given with RPV/FTC) When used with EVG/c/TDF/FTC, ↑ TDF and ledipasvir expected	Monitor for TDF-associated toxicities when coadministered with PI/r, PI/c, or EFV. Consider an alternative to PI/r plus TDF/FTC or alternative HCV therapy if possible. Do not co-administer with EVG/c/TDF/FTC. Consider TAF in place of TDF.
Linezolid	Rifabutin[a]	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy.
	Rifapentine[a]	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
Mefloquine	Clarithromycin	↑ Mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for mefloquine toxicity (e.g., QT prolongation).
	Erythromycin	↑ Mefloquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Mefloquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Rifapentine[a]	↓ Mefloquine expected	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Voriconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
Posaconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 10 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Posaconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole and HCV regimen-associated toxicities. Monitor posaconazole conc. and adjust dose if necessary.
	Elbasvir/grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ posaconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole and rifabutin conc. and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities (e.g., uveitis).
	Rifampin[a]	↓ Posaconazole expected	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	↓ Posaconazole expected	Co-administration should be avoided, if possible, or monitor posaconazole conc. and adjust dose accordingly; monitor clinical response.
	Simeprevir	↑ Simeprevir expected	Do not co-administer.
Quinine	Clarithromycin	↑ Quinine expected; ↑ clarithromycin possible	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Quinine expected; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Quinine expected; ↑ fluconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine and fluconazole toxicity (e.g., QT prolongation).
	Itraconazole	↑ Quinine expected; ↑ itraconazole possible	Co-administration should be avoided, if possible. If used concomitantly, monitor for quinine and itraconazole toxicity (e.g., QT prolongation), monitor itraconazole conc. and adjust dose accordingly.
	Posaconazole	↑ Quinine expected; ↑ posaconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Quinine possible; ↑ rifabutin possible	Monitor for quinine efficacy. Monitor rifabutin conc. and toxicity (e.g., uveitis).
	Rifampin[a]	Quinine AUC ↓ 75% to 85%	Do not co-administer.
	Rifapentine[a]	↓ Quinine expected	Do not co-administer.
	Voriconazole	↑ Quinine expected	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
Rifabutin[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 11 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Atovaquone	Atovaquone C_{SS} ↓ 34%; rifabutin C_{SS} ↓ 19%	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Bedaquiline	↓ Bedaquiline possible	If co-administered, monitor for bedaquiline efficacy.
	Caspofungin	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	Clarithromycin AUC ↓ by 44%; 14-OH AUC ↑ 57%; rifabutin AUC ↑ 76% to 99%; des-Rbt AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, consider reducing rifabutin dose, monitoring clarithromycin and rifabutin conc., and monitoring for rifabutin-associated toxicities (e.g., uveitis).
	Daclatasvir	↓ Daclatasvir expected	Dose not established. Consider increase daclatasvir dose to 90 mg once daily and monitoring for therapeutic efficacy.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Rifabutin expected; ↓ paritaprevir possible	Co-administration should be avoided if possible. With co-administration, decrease rifabutin dose to 150 mg/day and monitor rifabutin conc. Monitor HCV regimen for efficacy.
	Dapsone	Dapsone AUC ↓ 27% to 40%	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Doxycycline	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Elbasvir/Grazoprevir	↓ Elbasvir and grazoprevir possible	Co-administration should be avoided, if possible. Consider alternative HCV regimen.
	Erythromycin	↓ Erythromycin possible; ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy or rifabutin toxicities (e.g., uveitis).
	Fluconazole	Rifabutin AUC ↑ 80%; ↔ fluconazole	Use with caution. Monitor for rifabutin-associated toxicities (e.g., uveitis). Consider monitoring rifabutin conc.; may need to lower rifabutin dose to 150 mg/day.
	Itraconazole	Itraconazole AUC ↓ 70%; ↑ rifabutin expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Linezolid	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Mefloquine	↓ Mefloquine possible	Monitor for mefloquine efficacy.
	Posaconazole	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole and rifabutin conc. and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities (e.g., uveitis).
	Quinine	↓ Quinine possible; ↑ rifabutin possible	Monitor for quinine efficacy. Monitor rifabutin conc. and toxicity (e.g., uveitis).
	Simeprevir	↓ Simeprevir expected	Do not co-administer.
	Sofosbuvir	↓ Sofosbuvir expected	Do not co-administer.
	Velpatasvir/ Sofosbuvir	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 12 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	Voriconazole AUC ↓ 79%; rifabutin AUC ↑4-fold	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s). If coadministration is absolutely necessary, monitor voriconazole and rifabutin conc. to guide therapy.
Rifampin[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, and lumefantrine AUC by 89%, 85%, and 68%, respectively	Do not co-administer.
	Atovaquone	Atovaquone C_{ss} ↓ 52% and $t_{1/2}$ ↓ 40%; rifampin C_{ss} ↑ 37%	Do not co-administer.
	Bedaquiline	Bedaquiline AUC ↓ 53%	Do not co-administer.
	Caspofungin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be ↑ to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	Mean clarithromycin conc. ↓ 87%; rifampin AUC ↑ 60%	Do not co-administer. Use azithromycin in place of clarithromycin.
	Daclatasvir	Daclatasvir AUC ↓ 79%	Do not co-administer.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Dapsone	Dapsone conc. ↓ 7- to 10-fold and $t_{1/2}$ ↓ from 24 to 11 hours	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Doxycycline	Doxycycline AUC ↓ by 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
	Elbasvir/Grazoprevir	Grazoprevir AUC ↓ 7%, C_{24} ↓ 90%; ↓ elbasvir expected	Do not co-administer.
	Erythromycin	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Fluconazole	Fluconazole AUC ↓ by 23% to 56%	Monitor for antifungal efficacy. May need to increase fluconazole dose.
	Itraconazole	Itraconazole AUC ↓ 64% to 88%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	Ledipasvir AUC ↓ 59%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Linezolid	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy.
	Mefloquine	Mefloquine AUC ↓ 68%	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Posaconazole	↓ Posaconazole expected	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Quinine	Quinine AUC ↓ 75% to 85%	Do not co-administer.
	Simeprevir	Simeprevir C_{min} ↓92%, AUC ↓ 48%	Do not co-administer.
	Sofosbuvir	Sofosbuvir AUC ↓ 72%	Do not co-administer.
	Velpatasvir/ Sofosbuvir	Velpatasvir AUC ↓ 82%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Voriconazole	Voriconazole AUC ↓ 96%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 13 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifapentine[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, lumefantrine expected	Do not co-administer.
	Atovaquone	↓ Atovaquone expected	Do not co-administer.
	Bedaquiline	Bedaquiline AUC ↓ 55% (with daily rifapentine)	Do not co-administer.
	Caspofungin	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	↓ Clarithromycin expected; ↑ 14-OH and rifapentine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for rifapentine-associated toxicities, consider monitoring clarithromycin and rifapentine conc. and adjusting doses accordingly.
	Daclatasvir	↓ Daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitoring for therapeutic efficacy
	Dapsone	↓ Dapsone expected	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected.	Do not co-administer.
	Elbasvir/Grazoprevir	↓ Elbasvir and grazoprevir possible	Do not co-administer.
	Doxycycline	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Erythromycin	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Fluconazole	↓ Fluconazole expected	Monitor for antifungal efficacy; may need to ↑ fluconazole dose.
	Itraconazole	↓ Itraconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Linezolid	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Mefloquine	↓ Mefloquine expected	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Posaconazole	↓ Posaconazole expected	Co-administration should be avoided, if possible, or monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Quinine	↓ Quinine expected	Do not co-administer.
	Simprevir	↓ Simeprevir expected	Do not co-administer.
	Sofosbuvir	↓ Sofosbuvir expected	Do not co-administer.
	Velpatasvir/ Sofosbuvir	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 14 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↓ Voriconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
Simeprevir	Clarithromycin	↑ Simeprevir expected	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Daclatasvir	Simeprevir AUC ↑ 44%; daclatasvir AUC ↑ 96%	No dosage adjustment. Monitor for simeprevir- and daclatasvir-associated toxicities.
	Erythromycin	Simeprevir AUC ↑ 647%, C_{min} ↑ 1,174%; erythromycin AUC ↑ 90%, C_{min} ↑ 208%	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Fluconazole	↑ Simeprevir possible	Do not co-administer.
	Itraconazole	↑ Simeprevir expected	Do not co-administer.
	Ledipasvir/Sofosbuvir	Ledipasvir AUC ↑ 92%; simeprevir AUC ↑ 116%	Do not co-administer.
	Posaconazole	↑ Simeprevir expected	Do not co-administer.
	Rifabutin[a]	↓ Simeprevir expected	Do not co-administer.
	Rifampin[a]	Simeprevir C_{min} ↓ 92%, AUC ↓ 48%	Do not co-administer.
	Rifapentine[a]	↓ Simeprevir expected	Do not co-administer.
	Voriconazole	↑ Simeprevir expected	Do not co-administer.
Sofosbuvir	Rifabutin[a]	↓ Sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Sofosbuvir expected	Do not co-administer.
TAF	Ledipasvir/Sofosbuvir	Ledipasvir AUC ↑79%	No dosage adjustment.
	Velpatasvir/Sofosbuvir	TAF AUC ↓ 13%	No dosage adjustment.
TDF	Ledipasvir/Sofosbuvir	TDF AUC ↑ 98% (when given with EFV/FTC) TDF AUC ↑ 40% (when given with RPV/FTC) When used with EVG/c/TDF/FTC, ↑ TDF and ledipasvir expected	Monitor for TDF-associated toxicities when coadministered with PI/r, PI/c, or EFV. Consider an alternative to PI/r plus TDF/FTC or alternative HCV therapy if possible. Do not co-administer with EVG/c/TDF/FTC. Consider TAF in place of TDF.
	Velpatasvir/ Sofosbuvir	TDF AUC ↑35% to 40% when given with EVG/c/FTC or RPV/FTC TDF AUC ↑ 81% when given with EFV/FTC	Monitor for TDF-associated toxicities with PI/r or EFV co-administration. Consider TAF in place of TDF.
Velpatasvir/ Sofosbuvir	Rifabutin[a]	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Velpatasvir AUC ↓ 82%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.
	TAF	TAF AUC ↓ 13%	No dosage adjustment.
	TDF	TDF AUC ↑35% to 40% when given with EVG/c/FTC or RPV/FTC TDF AUC ↑ 81% when given with EFV/FTC	Monitor for TDF-associated toxicities with PI/r or EFV co-administration. Consider TAF in place of TDF.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 15 of 15)

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Voriconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	Voriconazole AUC ↓ 39% (with ritonavir); ↑ paritaprevir expected	Co-administer only if the benefits outweigh the risks. Monitor voriconazole conc. to guide dosage adjustments.
	Elbasvir/Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 4-fold	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s). If coadministration is absolutely necessary, monitor voriconazole and rifabutin conc. to guide therapy.
	Rifampin[a]	Voriconazole AUC ↓ 96%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	↓ Voriconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Simeprevir	↑ Simeprevir expected	Do not co-administer.

Key to Acronyms: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; C_{24} = concentration at 24h post dose; C_{min} = minimum concentration; C_{ss} = concentration at steady state; CYP3A4 = Cytochrome P450 3A4; des-Rbt = desacetyl rifabutin; DHA = dihydroartemisinin; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HCV = hepatitis C virus; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RPV = rilpivirine; $T_{1/2}$ = half-life; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate

[a] Rifamycins are potent inducers of Phase I and Phase II drug-metabolizing reactions. Daily doses of rifampin are well studied, and induction increases over a week or more. Based on limited data, larger doses of rifampin (for example, 1200 mg) appear to produce the same maximum induction, but more rapidly. Single doses of rifampin may not produce significant induction. In general, rifabutin is about 40% as potent a CYP3A4 inducer as rifampin, but this can vary by substrate and enzymatic reaction. In general, daily rifapentine (for active TB disease) is at least as potent an inducer as rifampin. However, the potential of drug interactions with once weekly rifapentine (for latent TB infection, along with isoniazid) is not well studied, but may result in reduction of exposure of drugs that are CYP3A4 substrates. When a rifamycin is used with a potential interacting drug, close monitoring for clinical efficacy of the other agent is advised.

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 1 of 6) (Last updated March 13, 2017; last reviewed March 13, 2017)

Drugs	Common or Serious Adverse Reactions
Acyclovir	Crystalluria (associated with high dose, dehydration, or pre-existing renal impairment), neurotoxicity (high doses, especially in patients with renal impairment and/or older adults; agitation, confusion, hallucination, seizure, coma), nephrotoxicity secondary to obstructive urolithiasis (particularly after rapid IV infusion), thrombophlebitis at peripheral IV infusion site, nausea, vomiting, headache
Adefovir	Nausea, asthenia, nephrotoxicity (especially in patients with underlying renal insufficiency or predisposing comorbidities, or in patients who are currently taking nephrotoxic drugs)
Albendazole	Nausea, vomiting, hepatotoxicity, hypersensitivity reaction, dizziness, headache, reversible alopecia Rarely: granulocytopenia, agranulocytosis, pancytopenia
Amikacin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), neuromuscular blockade (associated with rapid infusion of large aminoglycoside doses), pain upon IM injection
Amoxicillin/Clavulanate and Ampicillin/Sulbactam	Diarrhea, nausea, vomiting, abdominal pain, *Clostridium difficile*-associated diarrhea and colitis, hypersensitivity reactions (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, drug fever, neurotoxicity at high doses (especially in patients with renal dysfunction)
Amphotericin B Deoxycholate and Lipid Formulations	Nephrotoxicity, infusion-related reactions (fever, chills, rigors, back pain, hypotension), hypokalemia, hypomagnesemia, anemia, thrombophlebitis, nausea, vomiting Liposomal formulations have lower incidence of nephrotoxicity and infusion-related reactions.
Anidulafungin	Generally well-tolerated. Hepatotoxicity, histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea are rare if infusion rate <1.1 mg/min), hypokalemia, diarrhea
Artemether/Lumefantrine	Generally well-tolerated. Rash, pruritus, nausea, vomiting, abdominal pain, anorexia, diarrhea, arthralgia, myalgia, dizziness, asthenia, headache, hemolytic anemia (rare), QTc prolongation
Artesunate	Generally well-tolerated. Bradycardia, dizziness, nausea and vomiting, skin rash, pruritus, postartemisinin delayed hemolysis, QTc prolongation
Atovaquone	Rash, nausea, vomiting, diarrhea, hepatotoxicity, headache, hyperglycemia, fever
Atovaquone/Proguanil	Pruritus, rash, nausea, vomiting, abdominal pain, diarrhea, anorexia, erythema multiforme, asthenia, dizziness, headache, oral ulcers, hepatotoxicity
Azithromycin	Nausea, vomiting, diarrhea, hepatotoxicity, ototoxicity (with prolonged use), rash, urticaria, pruritus, abdominal pain, *C. difficile*-associated diarrhea, torsades de pointes (risk is greatest in patients with underlying QTc prolongation)
Aztreonam	Diarrhea, hypersensitivity reaction (rare), thrombophlebitis, neutropenia, increased liver enzymes, *C. difficile*-associated diarrhea
Benznidazole	Photosensitivity, allergic dermatitis, paresthesia, peripheral neuropathy, nausea, vomiting, abdominal pain, anorexia, weight loss
Bedaquiline	Nausea, arthralgia, headache, QTc prolongation, elevated transaminases
Capreomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), pain upon IM injection
Caspofungin	Generally well-tolerated. Fever, thrombophlebitis, histamine-related infusion reactions (flushing, rash, pruritus, facial swelling, hypotension, dyspnea), hypokalemia, anemia, headache, hepatotoxicity, diarrhea
Ceftriaxone	Generally well-tolerated. Cholelithiasis, urolithiasis, pancreatitis, rash, diarrhea, drug fever, hemolytic anemia, *C. difficile*-associated diarrhea and colitis, injection-site reactions after IM injections, pain

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 2 of 6)

Drugs	Common or Serious Adverse Reactions
Cephalosporins (for Ceftriaxone, see above)	Hypersensitivity reaction, rash, nausea, vomiting, diarrhea, C. difficile-associated diarrhea and colitis, bone marrow suppression, CNS toxicities such as seizure and confusion (rare, mostly seen with high doses used in patients with renal insufficiency or elderly patients without dosage adjustment), hemolytic anemia
Chloroquine and Hydroxychloroquine	Headache, pruritus, skin pigmentation, nausea, vomiting, abdominal pain, diarrhea, anorexia, photosensitivity, visual disturbances including blurry vision and retinal toxicity, auditory disturbances, QTc prolongation, cardiomyopathy, neuromyopathy (rare, but may occur with long-term use), bone marrow suppression, hemolysis (associated with G6PD deficiency), hypersensitivity reaction (including TEN, SJS, and EM), hepatitis, neuropsychiatric changes (including extrapyramidal reactions and suicidal behavior), convulsive seizures, severe hypoglycemia (may require adjustment of antidiabetic medications)
Cidofovir	Nephrotoxicity, proteinuria, ocular hypotony, anterior uveitis/iritis, neutropenia, metabolic acidosis (including Fanconi's syndrome), diarrhea, asthenia, fever, headache, alopecia, anemia Side effects most likely related to co-administration of probenecid: rash, nausea, vomiting, anorexia
Ciprofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with age >60 and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures, peripheral neuropathy
Clarithromycin	Hepatotoxicity, ototoxicity (with high doses or prolonged use), headache, nausea, vomiting, abdominal cramps, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, QTc prolongation, dysgeusia
Clindamycin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, arrhythmia associated with rapid IV infusion, metallic taste (with IV infusion), thrombophlebitis, abnormal liver function tests
Clotrimazole (Troche)	Generally well-tolerated. Nausea, vomiting, anorexia, metallic taste, increase in serum transaminases (rare)
Cycloserine	Neuropsychiatric toxicities (headache, somnolence, lethargy, vertigo, tremor, dysarthria, irritability, confusion, paranoia, psychosis), seizures (particularly in patients with history of chronic alcoholism), allergic dermatitis, rash, elevated transaminases, congestive heart failure (in patients receiving cycloserine 1-1.5 g daily)
Dapsone	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), neutropenia, dermatologic reactions (including rash), sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, hemolysis), peripheral neuropathy, hepatotoxicity, drug-induced lupus erythmatosus, nephrotic syndrome, phototoxicity
Daclatasvir	Fatigue, headache, nausea, anemia, bradycardia (when co-administered with sofosbuvir and amiodarone)
Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir	Hepatotoxicity, nausea, pruritus, rash, insomnia, fatigue, asthenia, dyspnea (associated with ribavirin co-administration)
Doxycycline	Photosensitivity reaction, nausea, vomiting, diarrhea, esophageal ulceration, thrombophlebitis (with IV infusion), hepatotoxicity (rare), intracranial hypertension, *C. difficile*-associated diarrhea and colitis, tissue hyperpigmentation
Elbasvir/Grazoprevir	Fatigue, headache, nausea, ALT elevations, anemia (when given with ribavirin)
Emtricitabine	Generally well-tolerated. Headache, nausea, skin hyperpigmentation, diarrhea, rash
Entecavir	Generally well-tolerated. Headache, fatigue, dizziness, nausea
Erythromycin	Nausea, vomiting, abdominal pain, anorexia, rash, hepatotoxicity, cholestatic jaundice, ototoxicity (hearing loss, tinnitus), rash, QTc prolongation and cardiac arrhythmia, *C. difficile*-associated diarrhea and colitis, thrombophlebitis (with IV infusion)

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 3 of 6)

Drugs	Common or Serious Adverse Reactions
Ethambutol	Optic neuritis (dose dependent), peripheral neuropathy, headache, nausea, vomiting, anorexia, hepatotoxicity, hyperuricemia, hypersensitivity reaction, disorientation, hallucinations
Ethionamide	Dose-dependent gastrointestinal side effects (nausea, vomiting, diarrhea, abdominal pain, metallic taste, anorexia), dizziness, drowsiness, depression, postural hypotension, hepatotoxicity, hypothyroidism (with or without goiter), gynecomastia, impotence, hypoglycemia
Famciclovir	Generally well-tolerated. Headache, nausea, vomiting, diarrhea, nephrotoxicity (in patients with underlying renal disease)
Flucytosine	Concentration-dependent bone marrow suppression (anemia, neutropenia, thrombocytopenia), diarrhea, nausea, vomiting, rash, hepatotoxicity
Fluconazole	Hepatotoxicity, rash, nausea, vomiting, diarrhea, abdominal discomfort, reversible alopecia (with doses ≥400 mg/d for >2 months), QTc prolongation
Foscarnet	Nephrotoxicity, electrolyte imbalances (hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia), penile ulceration, nausea, vomiting, anorexia, headache, seizure (associated with electrolyte imbalances), anemia, injection-site associated thrombophlebitis
Fumagillin (Investigational)	Oral therapy: Neutropenia, thrombocytopenia, vertigo, nausea, vomiting, diarrhea, anorexia, abdominal cramps Ocular therapy: Minimal systemic effect or local effect
Ganciclovir	Neutropenia, thrombocytopenia, anemia, injection-site-associated thrombophlebitis, increased serum creatinine, carcinogenic and teratogenic potential, impaired fertility, neuropathy
Imipenem/Cilastatin	Hypersensitivity reaction (immediate or delayed), nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, headache, bone marrow suppression, drug fever, CNS effects such as seizure, myoclonus, and confusion (especially with higher doses, in patients with underlying CNS disorders, or with renal insufficiency)
Interferon-Alfa and Peginterferon-Alfa	Flu-like syndrome (fever, headache, fatigue, and myalgia), neuropsychiatric disorders (depression and suicidal ideation), neutropenia, anemia, thrombocytopenia, thyroid dysfunction, injection-site reactions, alopecia, nausea, anorexia, diarrhea, weight loss, development or exacerbation of autoimmune disorders, ocular effects (retinal hemorrhage, retinal artery or vein obstructions, and cotton wool spots)
Isoniazid	Hepatotoxicity, peripheral neuropathy, optic neuritis, psychosis (rare), diarrhea, nausea
Itraconazole	Hepatotoxicity, congestive heart failure, edema, hypokalemia, nausea, vomiting, diarrhea, abdominal pain, rash, QTc prolongation, neuropathy
Lamivudine	Generally well-tolerated. Nausea, vomiting
Ledipasvir/Sofosbuvir	Fatigue, headache, asthenia (most common), nausea, diarrhea, insomnia, mild transient asymptomatic lipase elevation, mild bilirubin elevation
Levofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures (rare), peripheral neuropathy
Linezolid	Anemia, neutropenia, thrombocytopenia (especially with treatment lasting for longer than 2- to 4-weeks), peripheral neuropathy, optic neuritis with long-term therapy, serotonin syndrome (especially in patients receiving concomitant serotonergic agents), seizure (in patients with a history of seizure or with risk factors for seizure), lactic acidosis (rare), diarrhea, headache, nausea, vomiting
Mefloquine	Depression, psychosis, anxiety, rash (reports of TEN and SJS), nausea, vomiting, diarrhea, epigastric pain, agitation, dizziness, headache, insomnia, abnormal dreams, QTc prolongation, arrhythmias (extrasystole, sinus bradycardia), agranulocytosis/aplastic anemia

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 4 of 6)

Drugs	Common or Serious Adverse Reactions
Meropenem	Generally well-tolerated. Hypersensitivity reaction (immediate or delayed), nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, headache, bone marrow suppression, drug fever
Micafungin	Generally well-tolerated. Histamine-related infusion reactions (such as flushing, rash, pruritus, hypotension, dyspnea) may occur, but these are rare if infusion lasts over 1 hour; anaphylaxis and anaphylactoid reaction, hepatotoxicity, thrombophlebitis, nausea, vomiting, diarrhea, hypokalemia, hemolysis (rare)
Miconazole Buccal Tablets	Dysgeusia, diarrhea, nausea, vomiting, upper abdominal pain, headache, local reactions (oral discomfort, burning, pain, tongue/mouth ulceration, gingival pruritus, swelling, dry mouth), hypersensitivity reaction (rare—may occur in patients with known hypersensitivity reaction to milk product concentrate)
Miltefosine	Nausea, vomiting, diarrhea, headache, motion sickness, leukocytosis, thrombocytosis, nephrotoxicity, retinal degeneration, elevated transaminases and bilirubin, teratogenic potential, impaired fertility
Moxifloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures (rare), peripheral neuropathy
Nifurtimox	Anorexia, weight loss, nausea, vomiting, abdominal pain, headache, dizziness, mood changes, insomnia, myalgia, peripheral neuropathy, rash, pruritus, memory loss
Nitazoxanide	Generally well-tolerated. Nausea, vomiting, diarrhea, abdominal pain, headache
Nystatin (Oral Preparations)	Unpleasant taste, nausea, vomiting, anorexia, diarrhea, hypersensitivity reaction (rare)
Penicillin G	All Penicillin G Preparations: Hypersensitivity reactions (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, drug fever Benzathine Penicillin G and Procaine Penicillin G: IM injection-site reactions (pain and erythema), procaine neuropsychiatric reactions (high dose), neurovascular damage (as a result of inadvertent intravascular instead of IM injection) Aqueous Crystalline Penicillin G (IV): Thrombophlebitis, neurotoxicity at high doses (especially in patients with renal dysfunction)
Pentamidine	IV Infusion: Nephrotoxicity, infusion-related hypotension, thrombophlebitis, QTc prolongation, arrhythmias (including torsades de pointes), pancreatitis, hypoglycemia, hyperglycemia, diabetes mellitus, hepatotoxicity, electrolyte abnormalities, leucopenia, thrombocytopenia Aerosolized Therapy: Bronchospasm, cough, dyspnea, tachypnea, metallic taste, pancreatitis (rare)
Pentavalent Antimony (Sodium Stibogluconate)	Nausea, vomiting, abdominal pain, anorexia, pancreatitis (rare), headache, hepatotoxicity, arthralgia, myalgia, cardiac toxicity with higher than 20 mg/kg dose, rash, thrombophlebitis, leukopenia, anemia, thrombocytopenia
Posaconazole	Nausea, vomiting, diarrhea, abdominal pain, headache, hepatotoxicity, hypokalemia, QTc prolongation, rash IV Infusion: Thrombophlebitis, cyclodextrin accumulation (especially in patients with eGFR <50 mL/min, which may lead to renal toxicities)
Piperacillin-Tazobactam	Generally well-tolerated. Hypersensitivity reaction, rash, diarrhea, nausea, vomiting, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, thrombocytopenia (rare), impaired platelet aggregation, seizure (with high doses used in patients with renal insufficiency)
Primaquine	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), leukopenia, neutropenia, abdominal cramps, nausea, vomiting, QTc prolongation, pruritus, rash, dizziness

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 5 of 6)

Drugs	Common or Serious Adverse Reactions
Pyrimethamine	Neutropenia, thrombocytopenia, megaloblastic anemia, rash
Quinidine Glucuronate	QTc prolongation, lightheadedness, nausea, vomiting, diarrhea, abdominal pain, drug-induced SLE, headache, rash, hemolysis (with G6PD deficiency), hepatotoxicity, heartburn/esophagitis, cinchonism (tinnitus, vertigo, blurred vision)
Quinine	Headache, nausea, vomiting, diarrhea, cinchonism (tinnitus, vertigo, blurred vision), hypersensitivity reaction, hypoglycemia, thrombocytopenia, QTc prolongation
Ribavirin	Hemolytic anemia, dyspnea, hyperbilirubinemia, fatigue, myalgia, headache, nausea, vomiting, anorexia, dyspepsia, rash, dry cough, teratogenicity, hypersensitivity reaction, hepatotoxicity
Rifabutin	Hepatotoxicity, uveitis (dose dependent), red-orange discoloration of body fluids, rash, arthralgia, neutropenia, nausea, vomiting, abdominal pain, diarrhea, anorexia
Rifampin	Hepatotoxicity (cholestatic hepatitis), red-orange discoloration of body fluids, thrombocytopenia, hemolytic anemia, rash, hypersensitivity reactions with flu-like syndrome, nausea, vomiting, anorexia, abdominal pain, flatulence, diarrhea, renal failure, headache, confusion
Rifapentine	Hypersensitivity reaction, hepatotoxicity, anemia, lymphopenia, neutropenia, arthralgia, conjunctivitis, headache, vomiting, nausea, diarrhea, rash, pruritus, anorexia and lymphadenopathy, red-orange discoloration of body fluids, *C. difficile*-associated diarrhea and colitis
Simeprevir	Rash and pruritus (generally mild in severity, but severe rashes have been reported), photosensitivity reaction, direct and indirect asymptomatic hyperbilirubinemia without elevation in AST/ALT, mild dyspnea, headache, fatigue, insomnia, dizziness, nausea
Sofosbuvir	Generally well-tolerated. Fatigue, headache, nausea, insomnia, anemia, bilirubin elevation (associated with ribavirin co-administration), asymptomatic CK elevation and lipase elevation, pancytopenia, depression (associated with Peg-IFN co-administration)
Streptomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), other severe neurotoxic reactions (mostly in patients with impaired renal function), pain upon IM injection, eosinophilia, *C. difficile*-associated diarrhea and colitis
Sulfadiazine	Rash (including SJS, EM, TEN), anemia, neutropenia, thrombocytopenia, crystalluria (with or without urolithiasis), renal insufficiency, nausea, vomiting, drug fever, hepatotoxicity, headache, peripheral neuritis, tinnitus, vertigo, insomnia
Telbivudine	Generally well-tolerated. Nausea, vomiting, abdominal pain, increase in creatine kinase, headache, dizziness, fatigue, diarrhea, myopathy, myalgia, cough, fever, dyspepsia, abdominal pain
Tenofovir DF	Renal insufficiency, proximal renal tubulopathy (with hypophosphatemia, hypouricemia, normoglycemic glycosuria), decrease in bone mineral density, nausea
Tenofovir Alafenamide	Less renal or bone toxicities compared to tenofovir DF
Tetracycline	Photosensitivity, tooth discoloration if taken by infants and children, reduced skeletal development, pruritus, esophageal ulceration, nausea, vomiting, diarrhea, hepatotoxicity, rash, increased BUN, intracranial hypertension
Trimethoprim-Sulfamethoxazole	Rash (including SJS, EM, and TEN), photosensitivity, anemia, neutropenia, thrombocytopenia, hepatotoxicity, increase in serum creatinine (without change in GFR), interstitial nephritis, nausea, vomiting, crystalluria (in patients with inadequate hydration), hyperkalemia (more common with high-dose TMP), drug fever
Valacyclovir	Generally well-tolerated. Nausea, vomiting, headache, crystalluria (with high dose or renal impairment), neurotoxicity (with high doses, especially in patients with renal impairment; agitation, confusion, hallucination, seizure, coma), abdominal pain
Valganciclovir	Neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, confusion, pyrexia, tremor, acute renal failure, carcinogenic and teratogenic potential, impaired fertility
Vancomycin	Infusion-related reactions (associated with infusion rate and can include flushing, hypotension, and rash), thrombophlebitis, rash, neutropenia, thrombocytopenia (rare), ototoxicity (associated with excessive concentration), nephrotoxicity (associated with high daily dose and high trough concentrations)

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 6 of 6)

Drugs	Common or Serious Adverse Reactions
Velpatasvir/Sofosbuvir	Headache, fatigue
Voriconazole	Visual disturbances (associated with initial dosing), optic neuritis (associated with >28 days treatment), skin photosensitivity, hepatotoxicity, fever, nausea, rash, vomiting, chills, tachycardia, QTc prolongation, peripheral edema, headache, delirium, hallucination, encephalopathy (associated with trough >5.5 mcg/mL), peripheral neuropathy (rare), fluorosis and periotitis with high dose and/or prolonged use, cyclodextrin accumulation (associated with use of IV formulation in patients with CrCl <50 mL/min, which may lead to renal toxicities)

Key to Acronyms: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CNS = central nervous system; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; EM = erythema multiforme; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; IM = intramuscular; IV = intravenous; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus; TEN = toxic epidermal necrolysis; TMP = trimethoprim

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 1 of 7)
(Last updated May 7, 2013; last reviewed May 7, 2013)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Acyclovir	IV dose for: • serious HSV - 5 mg/kg IV q8h, *or* • VZV infections - 10 mg/kg IV q8h	25–50	100% of dose IV q12h
		10–25	100% of dose IV q24h
		<10	50% of dose IV q24h
		hemodialysis	50% of dose q24h; administer after dialysis on day of dialysis
	PO Dose for Herpes Zoster: 800 mg PO 5 times/day	10–25	800 mg PO q8h
		<10	800 mg PO q12h
		hemodialysis	800 mg PO q12h; administer dose after dialysis
Adefovir	10 mg PO q24h	30–49	10 mg PO q48h
		10–29	10 mg PO q72h
		hemodialysis	10 mg PO weekly (dose after dialysis)
Amikacin (for mycobacterial infections)	IV 15 mg/kg/day or 25 mg/kg TIW	Use with caution in patients with renal insufficiency.	Adjust dose based on serum concentrations with target peak concentration 35–45 mcg/mL and trough concentration <4 mcg/mL.
Amphotericin B	• 0.7–1.0 mg/kg/day IV (amphotericin B deoxycholate), *or* • 3–6 mg/kg/day IV (lipid formulation)		No dosage adjustment necessary; alternative antifungals should be considered if renal insufficiency occurs during therapy despite adequate hydration.
Capreomycin	15 mg/kg (maximum dose 1000 mg) IV or IM per day	Use with caution in patients with renal insufficiency.	Refer to product label for dosing guidelines based on creatinine clearance. Consider monitoring capreomycin serum concentrations.
Chloroquine (base)	For Treatment of Acute Malaria: • 600 mg PO for 1 dose, followed by 300 mg PO at 6, 24, and 48 hours (for a total dose of 1500 mg)	<10	50% of dose
Cidofovir	• 5 mg/kg IV on days 0, repeat 5 mg/kg IV dose at day 7, then 5 mg/kg IV every 2 weeks (days 21, 35, 49, 63, etc.) Each dose should be given with probenecid and saline hydration (see Table 2).	• Pretreatment SCr >1.5 mg/dL, *or* • CrCl < 55 mL/min, *or* • >100 mg/dL (>2+) protein in urinalysis	Cidofovir is not recommended
		If SCr increases by 0.3–0.4 mg/dL from baseline	3 mg/kg IV per dose
		• If SCr increases >0.5 mg/dL >baseline, *or* • ≥3+ proteinuria	Discontinue therapy

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 2 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Ciprofloxacin	• 500–750 mg PO q12h, *or* • 400 mg IV q8–12h	<30	250–500 mg PO q24h *or* 400 mg IV q24h
		hemodialysis or peritoneal dialysis	250–500 mg PO q24hr *or* 200–400 mg IV q24h (administered after dialysis)
Clarithromycin	500 mg PO BID	<30	250 mg PO BID or 500 mg PO once daily
Cycloserine	10 mg/kg/day PO in 2 divided doses (maximum 1000 mg/day)	50–80	Normal dose, consider monitoring serum concentration and toxicities
		<50 (not on hemodialysis)	Not recommended because of accumulation and toxicities.
		hemodialysis	250 mg PO once daily or 500 mg PO TIW—consider monitoring serum cycloserine concentration
Emtricitabine	• 200–mg tablet PO once daily, *or* • 240–mg solution PO once daily		Oral Tablets / Oral Solution
		30–49	200 mg q48h / 120 mg q24h
		15–29	200 mg q72h / 80 mg q24h
		<15 or hemodialysis (dose after dialysis)	200 mg q96h / 60 mg q24h
Emtricitabine/ Tenofovir (co-formulation as Truvada) Please refer to product information for dosing recommendations for other ARV fixed dose combination product containing tenofovir/ emtricitabine.	200 mg/300 mg - 1 tablet PO daily	30–49	1 tablet PO q48h (monitor for worsening renal function; consider alternative to TDF)
		<30 or hemodialysis	Co-formulated tablet should not be used for CrCl <30 mL/min. Use individual formulation and adjust dose according to recommendations for individual drugs.

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 3 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Entecavir	Usual Dose: • 0.5 mg PO once daily For Treatment of 3TC-Refractory HBV or for Patients with Decompensated Liver Disease: • 1 mg PO once daily		Usual Dose	3TC-Refractory or Decompensated Liver Disease
		30 to <50	• 0.25 mg q24h, *or* • 0.5 mg q48h	• 0.5 mg q24h, *or* • 1 mg q48h
		10 to <30	• 0.15 mg q24h, *or* • 0.5 mg q72h	• 0.3 mg q24h, *or* • 1 mg q72h
		<10 or hemodialysis or CAPD (administer after dialysis on dialysis day)	• 0.05 mg q24h, *or* • 0.5 mg q7 days	• 0.1 mg q24h, *or* • 1 mg q7 days
Ethambutol	• 15–25 mg/kg PO daily • (15 mg/kg PO daily for MAI; 15–25 mg/kg PO daily for MTB)	10–50	15–25 mg/kg q24–36h	
		<10	15–25 mg/kg q48h	
		hemodialysis	15–25 mg/kg TIW after hemodialysis Can consider TDM to guide optimal dosing	
Famciclovir	For Herpes Zoster: • 500 mg PO q8h	40–59	500 mg PO q12h	
		20–39	500 mg PO q24h	
		<20	250 mg PO q24h	
		hemodialysis	250 mg PO after each dialysis	
Fluconazole	200–1200 mg PO or IV q24h	≤50	50% of dose q24h	
		hemodialysis	Full dose after each dialysis	
Flucytosine	25 mg/kg PO q6h If available, TDM is recommended for all patients to guide optimal dosing (goal peak 30–80 mcg/mL 2 hour post dose)	20–40	25 mg/kg q12h	
		10–20	25 mg/kg q24h	
		<10	25 mg/kg q48h	
		hemodialysis	25–50 mg/kg q48–72h (after hemodialysis)	
Foscarnet	180 mg/kg/day IV in 2 divided doses for induction therapy for CMV infection 90–120 mg/kg IV once daily for maintenance therapy for CMV infection or for treatment of HSV infections	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.		

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 4 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Ganciclovir	Induction Therapy: • 5 mg/kg IV q12h	50–69	2.5 mg/kg IV q12h	
		25–49	2.5 mg/kg IV q24h	
		10–24	1.25 mg/kg IV q24h	
		<10 or on hemodialysis	1.25 mg/kg IV TIW after dialysis	
	Maintenance Therapy: • 5 mg/kg IV q24h	50–69	2.5 mg/kg IV q24h	
		25–49	1.25 mg/kg IV q24h	
		10–24	0.625 mg/kg IV q24h	
		<10 or on hemodialysis	0.625 mg/kg IV TIW after dialysis	
Lamivudine	300 mg PO q24h	30–49	150 mg PO q24h	
		15–29	150 mg PO once, then 100 mg PO q24h	
		5–14	150 mg PO once, then 50 mg PO q24h	
		<5 or on hemodialysis	50 mg PO once, then 25 PO mg q24h (give the dose after dialysis on dialysis day)	
Levofloxacin	500 mg (low dose) or 750 mg (high dose) IV or PO daily Nosocomial Pneumonia/ Osteomyelitis: • 750 mg daily	20–49	Lower Dose 500 mg once, then 250 mg q24h	High Dose 750 mg q48h
		<19 or on CAPD or hemodialysis (dose after dialysis)	500 mg once, then 250 mg q48h	750 mg once, then 500 mg q48h
Peginterferon Alfa-2a	180 mcg SQ once weekly	<30	135 mcg SQ once weekly	
		hemodialysis		
Peginterferon Alfa-2b	1.5 mcg/kg SQ once weekly	30–50	Reduce dose by 25%	
		10–29 and hemodialysis	Reduce dose by 50%	
Penicillin G Potassium (or sodium)	Neurosyphilis or Ocular/Otic Syphilis: • 3–4 million units IV q4h, *or* • 18–24 million units IV daily as continuous infusion	10–50	2–3 million units q4h or 12–18 million units as continuous infusion	
		<10	2 million units q4–6h or 8–12 million units as continuous infusion	
		hemodialysis or CAPD	2 million units q6h or 8 million units as continuous infusion	
Pentamidine	4 mg/kg IV q24h	10–50	3 mg/kg IV q24h	
		<10	4 mg/kg IV q48h	

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 5 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Pyrazinamide	See Table 3 for weight-based dosing guidelines	<10	50% of usual dose
		hemodialysis	Usual dose given after dialysis
Quinidine Gluconate (salt) (10 mg quinidine gluconate salt = 6.25 mg quinidine base)	Loading Dose: • 10 mg/kg (salt) IV over 1–2 hours, then 0.02 mg/kg/min (salt) IV for up to 72 hours or until able to take PO meds Consider TDM for all patients to optimize dosing.	<10	75% of normal dose
		hemodialysis	75% of normal dose; some clinicians recommend supplementation with 100 mg–200 mg after dialysis.
Quinine Sulfate	650 mg salt (524 mg base) PO q8h	<10 or hemodialysis	650 mg once, then 325 mg PO q12h
Ribavirin	For genotypes 1 and 4: • 1000–1200 mg PO per day in 2 divided doses (based on weight, see Table 2 for full dosing recommendation) For genotype 2 and 3: • 400 mg PO BID for genotypes 2 and 3	30–50	Alternate dosing 200 mg PO and 400 mg PO every other day
		<30 or hemodialysis	200 mg PO daily
Rifabutin	300 mg PO daily (see Table 5 for dosage adjustment based on drug-drug interaction)	<30	50% of dose once daily. Consider TDM
Streptomycin	• 15 mg/kg IM or IV q24h, *or* • 25 mg/kg IM or IV TIW	Use with caution in patients with renal insufficiency.	Adjust dose based on serum concentrations.
Sulfadiazine	1000–1500 mg PO q6h (1500 mg q6h for >60kg)	10–50	1000–1500 mg PO q12h (ensure adequate hydration)
		<10 or hemodialysis	1000–1500 mg PO q24h (dose after HD on days of dialysis)
Telbivudine	600 mg PO daily	30–49	Oral tablets: 600 mg PO q48h Oral solution: 400 mg PO q24h
		<30	Oral tablets: 600 mg PO q72h Oral solution: 200 mg PO q24h
		hemodialysis	Oral tablets: 600 mg PO q96h (dose after dialysis) Oral solution: 120 mg PO q24h (dose after dialysis on dialysis day)

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 6 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Tenofovir	300 mg PO daily	30–49	300 mg PO q48h	
		10–29	300 mg PO q72–96h	
		<10 and not on dialysis	Not recommended	
		hemodialysis	300 mg PO once weekly (dose after dialysis) Can consider alternative agent for treatment of HBV and/or HIV if TDF-associated renal toxicity occurs.	
Tetracycline	250 mg PO q6h Consider using doxycycline in patients with renal dysfunction.	10–49	250 mg PO q12–24h	
		<10	250 mg PO q24h	
		hemodialysis	250 mg PO q24h; dose after dialysis	
Trimethoprim/ Sulfamethoxazole	For PCP Treatment: • 5 mg/kg (of TMP component) IV q8h, *or* • 2 DS tablets PO q8h	10–30	5 mg/kg (TMP) IV q12h or TMP-SMX 2 DS tablets PO q12h	
		<10	5 mg/kg (TMP) IV q24h, or TMP-SMX DS tablet PO q12h (or 2 TMP-SMX DS tablets q24h)	
		hemodialysis	5 mg/kg/day (TMP) IV or 2 TMP-SMX DS tablets PO; dose after dialysis on dialysis day Can consider TDM to optimize therapy (target TMP concentrations: 5–8 mcg/mL)	
Valacyclovir	For Herpes Zoster: • 1 g PO TID	30–49	1 g PO q12h	
		10–29	1 g PO q24h	
		<10	500 mg PO q24h	
		hemodialysis	500 mg PO q24h; dose after dialysis on dialysis days	
Valganciclovir	Induction Therapy: • 900 mg PO BID Maintenance Therapy: • 900 mg PO daily		Induction	Maintenance
		40–59	450 mg PO BID	450 mg PO daily
		25–39	450 mg PO daily	450 mg PO q48h
		10–25	450 mg PO q48h	450 mg PO BIW
		<10 not on dialysis	not recommended	not recommended
		hemodialysis (clinical efficacy of this dosage has not been established)	200 mg PO TIW after dialysis (oral powder formulation)	100 mg PO TIW after dialysis (oral powder formulation)

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 7 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Voriconazole	• 6 mg/kg IV q12h 2 times, then 4 mg/kg q12h, *or* • 200–300 mg PO q12h	<50	IV voriconazole is not recommended because of potential toxicity due to accumulation of sulfobutylether cyclodexrin (vehicle of IV product). Should switch to PO voriconazole in these patients. No need for dosage adjustment when PO dose is used.

Key to Acronyms: 3TC = lamivudine; BID = twice daily; BIW = twice weekly; CAPD = continuous ambulatory peritoneal dialysis; CMV = cytomegalovirus; CrCl = creatinine clearance; DS = double strength, HBV = hepatitis B virus; HSV = herpes simplex virus; IM = intramuscular; IV = intravenous; MAI = *Mycobacterium avium intracellulare*; MTB = *Mycobacterium tuberculosis*; PCP = *Pneumocystis* pneumonia; PO = orally; q(n)h = every "n" hours; SQ = subcutaneous; SCr = ; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TID = three times daily; TIW = three times weekly; TMP = trimethoprim; SMX = sulfamethoxazole; VZV = varicella zoster virus

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{Serum Creatinine}}$	Female: $\frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{Serum Creatinine}}$

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 1 of 9) (Last updated October 28, 2014; last reviewed October 28, 2014)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Acyclovir	B	No teratogenicity in mice, rats, rabbits at human levels. Large experience in pregnancy (>700 first-trimester exposures reported to registry); well-tolerated.	Treatment of frequent or severe symptomatic herpes outbreaks or varicella
Adefovir	C	No increase in malformations at 23 times (rats) and 40 times (rabbits) human dose. Limited experience with human use in pregnancy.	Not recommended because of limited data in pregnancy. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com
Albendazole	C	Embryotoxic and teratogenic (skeletal malformations) in rats and rabbits, but not in mice or cows. Limited experience in human pregnancy.	Not recommended, especially in first trimester. Primary therapy for microsporidiosis in pregnancy should be ART.
Amikacin	C	Not teratogenic in mice, rats, rabbits. Theoretical risk of ototoxicity in fetus; reported with streptomycin but not amikacin.	Drug-resistant TB, severe MAC infections
Amoxicillin, amox./ clavulanate, ampicillin/sulbactam	B	Not teratogenic in animals. Large experience in human pregnancy does not suggest an increase in adverse events.	Susceptible bacterial infections
Amphotericin B	B	Not teratogenic in animals or in human experience. Preferred over azole antifungals in first trimester if similar efficacy expected.	Documented invasive fungal disease
Antimonials, pentavalent (stibogluconate, meglumine)	Not FDA approved	Antimony not teratogenic in rats, chicks, sheep. Three cases reported of use in human pregnancy in second trimester with good outcome. Labeled as contraindicated in pregnancy.	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine
Artesunate, artemether, artemether/ lumefantrine	C	Embryotoxicity, cardiovascular and skeletal anomalies in rats and rabbits. Embryotoxic in monkeys. Human experience, primarily in the second and third trimesters, has not identified increased adverse events.	Recommended by WHO as first-line therapy in second/third trimester for *P. falciparum* and severe malaria. Pending more data, use for malaria in first trimester only if other drugs not available or have failed. Report cases of exposure to WHO Anti-malarial Pregnancy Exposure Registry when available.
Atovaquone	C	Not teratogenic in rats or rabbits, limited human experience	Alternate agent for PCP, *Toxoplasma gondii*, malaria infections
Azithromycin	B	Not teratogenic in animals. Moderate experience with use in human pregnancy does not suggest adverse events.	Preferred agent for MAC prophylaxis or treatment (with ethambutol), *Chlamydia trachomatis* infection in pregnancy.
Aztreonam	B	Not teratogenic in rats, rabbits. Limited human experience, but other beta-lactam antibiotics have not been associated with adverse pregnancy outcomes.	Susceptible bacterial infections
Bedaquiline	B	Not teratogenic in rats, rabbits. No experience in human pregnancy.	Multidrug resistant TB when effective treatment regimen can not otherwise be provided.
Benznidazole	Not FDA approved	No animal studies. Increase in chromosomal aberrations in children with treatment; uncertain significance. No human pregnancy data.	Not indicated for chronic *T. cruzi* in pregnancy. Seek expert consultation if acute or symptomatic infection in pregnancy requiring treatment.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 2 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Boceprevir	B	Not teratogenic in rats, rabbits. No human pregnancy data.	Treatment of HCV currently generally not indicated in pregnancy.
Capreomycin	C	Increase in skeletal variants in rats. Limited experience in human pregnancy; theoretical risk of fetal ototoxicity.	Drug-resistant TB
Caspofungin	C	Embryotoxic, skeletal defects in rats, rabbits. No experience with human use.	Invasive *Candida* or *Aspergillus* infections refractory to amphotericin and azoles
Cephalosporins	B	Not teratogenic in animals. Large experience in human pregnancy has not suggested increase in adverse outcomes.	Bacterial infections; alternate treatment for MAC
Chloroquine	C	Associated with anophthalmia, micro-ophthalmia at fetotoxic doses in animals. Not associated with increased risk in human pregnancy at doses used for malaria.	Drug of choice for malaria prophylaxis and treatment of sensitive species in pregnancy.
Cidofovir	C	Embryotoxic and teratogenic (meningocele, skeletal abnormalities) in rats and rabbits. No experience in human pregnancy.	Not recommended
Ciprofloxacin, other quinolones	C	Arthropathy in immature animals; not embryotoxic or teratogenic in mice, rats, rabbits, or monkeys. More than 1100 cases of quinolone use in human pregnancy have not been associated with arthropathy or birth defects.	Severe MAC infections; multidrug resistant TB, anthrax, bacterial infections
Clarithromycin	C	Cardiovascular defects noted in one strain of rats and cleft palate in mice at high doses, not teratogenic in rabbits or monkeys. Two human studies, each with >100 first-trimester exposures, did not show increase in defects but one study found an increase in spontaneous abortion.	Treatment or secondary MAC prophylaxis, if other choices exhausted
Clindamycin	B	No concerns specific to pregnancy in animal or human studies.	Treatment of anaerobic bacterial infections and used with quinine for chloroquine-resistant malaria; alternate agent for secondary prophylaxis of *Toxoplasma* encephalitis
Clofazimine	C	Not teratogenic in mice, rats, or rabbits. Limited experience reported (19 cases); no anomalies noted but red-brown skin discoloration reported in several infants exposed throughout pregnancy.	No indications.
Clotrimazole troches	C	Not teratogenic in animals at exposures expected from treatment of oral or vaginal *Candida*. No increase in adverse pregnancy outcomes with vaginal use.	Oral or vaginal *Candida* infections and prophylaxis
Cycloserine	C	Not teratogenic in rats. No data available from human studies.	Drug-resistant TB

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 3 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Dapsone	C	No animal data. Limited human experience does not suggest teratogenicity; might displace bound bilirubin in the neonate, increasing the risk of kernicterus. Case reports of hemolytic anemia in fetus/infant with maternal treatment.	Alternate choice for primary or secondary PCP prophylaxis
Diphenoxylate	C	Limited animal and human data do not indicate teratogenicity.	Symptomatic treatment of diarrhea
Doxycycline, other tetracyclines	D	Risk of hepatic toxicity increased with tetracyclines in pregnancy; staining of fetal bones and teeth contraindicates use in pregnancy.	No indications
Emtricitabine	B	No concerns in pregnancy from limited animal and human data.	As part of fully suppressive combination antiretroviral regimen for treatment of HIV, HBV. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Entecavir	C	Animal data do not suggest teratogenicity at human doses; limited experience in human pregnancy.	Not recommended because of limited data in pregnancy. Use as part of fully suppressive ARV regimen with ARV agents active against both HIV and HBV. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Erythromycin	B	Hepatotoxicity with erythromycin estolate in pregnancy; other forms acceptable; no evidence of teratogenicity	Bacterial and chlamydial infections
Ethambutol	B	Teratogenic, at high doses, in mice, rats, rabbits. No evidence of teratogenicity in 320 cases of human use for treatment of TB.	Active TB and MAC treatment; avoid in first trimester if possible
Ethionamide	C	Increased rate of defects (omphalocele, exencephaly, cleft palate) in rats, mice, and rabbits with high doses; not seen with usual human doses. Limited human data; case reports of CNS defects.	Active TB; avoid in first trimester if possible
Famciclovir	B	No evidence of teratogenicity in rats or rabbits, limited human experience.	Recurrent genital herpes and primary varicella infection. Report exposures during pregnancy to the Famvir Pregnancy Registry (1-888-669-6682).
Fluconazole	C	Abnormal ossification, structural defects in rats, mice at high doses. Case reports of rare pattern of craniofacial, skeletal and other abnormalities in five infants born to four women with prolonged exposure during pregnancy; no increase in defects seen in several series after single dose treatment.	Single dose may be used for treatment of vaginal *Candida* though topical therapy preferred. Not recommended for prophylaxis during early pregnancy. Can be used for invasive fungal infections after first trimester; amphotericin B preferred in first trimester if similar efficacy expected.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 4 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Flucytosine	C	Facial clefts and skeletal defects in rats; cleft palate in mice, no defects in rabbits. No reports of use in first trimester of human pregnancy; may be metabolized to 5-fluorouracil, which is teratogenic in animals and possibly in humans.	Use after first trimester if indicated for life-threatening fungal infections.
Foscarnet	C	Skeletal variants in rats, rabbits and hypoplastic dental enamel in rats. Single case report of use in human pregnancy in third trimester.	Alternate agent for treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection.
Fumagillin	Not FDA approved	Caused complete litter destruction or growth retardation in rats, depending on when administered. No data in human pregnancy.	Topical solution can be used for ocular microsporidial infections.
Ganciclovir, valganciclovir	C	Embryotoxic in rabbits and mice; teratogenic in rabbits (cleft palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus). Case reports of safe use in human pregnancy after transplants, treatment of fetal CMV.	Treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection. Preferred agent for therapy in children.
Imipenem, meropenem	C/B	Not teratogenic in animals; limited human experience.	Serious bacterial infections
Imiquimod	B	Not teratogenic in rats and rabbits; 8 case reports of human use, only 2 in first trimester.	Because of limited experience, other treatment modalities such as cryotherapy or trichloracetic acid recommended for wart treatment during pregnancy.
Influenza vaccine	C	Not teratogenic. Live vaccines, including intranasal influenza vaccine, are contraindicated in pregnancy.	All pregnant women should receive injectable influenza vaccine because of the increased risk of complications of influenza during pregnancy. Ideally, HIV-infected women should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Interferons (alfa, beta, gamma)	C	Abortifacient at high doses in monkeys, mice; not teratogenic in monkeys, mice, rats, or rabbits. Approximately 30 cases of use of interferon-alfa in pregnancy reported; 14 in first trimester without increase in anomalies; possible increased risk of intrauterine growth retardation.	Not indicated. Treatment of HCV currently generally not recommended in pregnancy.
Isoniazid	C	Not teratogenic in animals. Possible increased risk of hepatotoxicity during pregnancy; prophylactic pyridoxine, 50 mg/day, should be given to prevent maternal and fetal neurotoxicity.	Active TB; prophylaxis for exposure or skin test conversion

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 5 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Itraconazole	C	Teratogenic in rats and mice at high doses. Case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy; no increase in defect rate noted among over 300 infants born after first-trimester itraconazole exposure.	Only for documented systemic fungal disease, not prophylaxis. Consider using amphotericin B in first trimester if similar efficacy expected.
Kanamycin	D	Associated with club feet in mice, inner ear changes in multiple species. Hearing loss in 2.3% of 391 children after long-term *in utero* therapy.	Drug-resistant TB
Ketoconazole	C	Teratogenic in rats, increased fetal death in mice, rabbits. Inhibits androgen and corticosteroid synthesis; may impact fetal male genital development; case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy.	None
Lamivudine	C	Not teratogenic in animals. No evidence of teratogenicity with >3700 first-trimester exposures reported to Antiretroviral Pregnancy Registry.	HIV and HBV therapy, only as part of a fully suppressive combination ARV regimen. Report exposures to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Ledipasvir/sofusbuvir	B	No evidence of teratogenicity in rats or rabbits. No experience in human pregnancy	Treatment of hepatitis C generally not indicated in pregnancy.
Leucovorin (folinic acid)	C	Prevents birth defects of valproic acid, methotrexate, phenytoin, aminopterin in animal models. No evidence of harm in human pregnancies.	Use with pyrimethamine if use of pyrimethamine cannot be avoided.
Linezolid	C	Not teratogenic in animals. Decreased fetal weight and neonatal survival at ~ human exposures, possibly related to maternal toxicity. Limited human experience.	Serious bacterial infections
Loperamide	B	Not teratogenic in animals. No increase in birth defects among infants born to 89 women with first-trimester exposure in one study; another study suggests a possible increased risk of hypospadias with first-trimester exposure, but confirmation required.	Symptomatic treatment of diarrhea after the first trimester
Mefloquine	C	Animal data and human data do not suggest an increased risk of birth defects, but miscarriage and stillbirth may be increased.	Second-line therapy of chloroquine-resistant malaria in pregnancy, if quinine/clindamycin not available or not tolerated. Weekly as prophylaxis in areas with chloroquine-resistant malaria.
Meglumine	Not FDA approved	See **Antimonials, pentavalent**	
Metronidazole	B	Multiple studies do not indicate teratogenicity. Studies on several hundred women with first-trimester exposure found no increase in birth defects.	Anaerobic bacterial infections, bacterial vaginosis, trichomoniasis, giardiasis, amebiasis

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 6 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Micafungin	C	Teratogenic in rabbits; no human experience.	Not recommended
Miltefosine	Not FDA approved	Embryotoxic in rats, rabbits; teratogenic in rats. No experience with human use.	Not recommended
Nifurtimox	Not FDA approved	Not teratogenic in mice and rats. Increased chromosomal aberrations in children receiving treatment; uncertain significance. No experience in human pregnancy.	Not indicated in chronic infection; seek expert consultation if acute infection or symptomatic reactivation of *T. cruzi* in pregnancy.
Nitazoxanide	B	Not teratogenic in animals; no human data	Severely symptomatic cryptosporidiosis after the first trimester
Para-amino salicylic acid (PAS)	C	Occipital bone defects in one study in rats; not teratogenic in rabbits. Possible increase in limb, ear anomalies in one study with 143 first-trimester exposures; no specific pattern of defects noted, several studies did not find increased risk.	Drug-resistant TB
Paromomycin	C	Not teratogenic in mice and rabbits. Limited human experience, but poor oral absorption makes toxicity, teratogenicity unlikely.	Amebic intestinal infections, possibly cryptosporidiosis
Penicillin	B	Not teratogenic in multiple animal species. Vast experience with use in human pregnancy does not suggest teratogenicity, other adverse outcomes.	Syphilis, other susceptible bacterial infections
Pentamidine	C	Embryocidal but not teratogenic in rats, rabbits with systemic use. Limited experience with systemic use in pregnancy.	Alternate therapy for PCP and leishmaniasis.
Piperacillin-tazobactam	B	Not teratogenic in limited animal studies. Limited experience in pregnancy but penicillins generally considered safe.	Bacterial infections
Pneumococcal vaccine	C	No studies in animal pregnancy. Polysaccharide vaccines generally considered safe in pregnancy. Well-tolerated in third-trimester studies.	Initial or booster dose for prevention of invasive pneumococcal infections. HIV-infected pregnant women should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Podophyllin, podofilox	C	Increased embryonic and fetal deaths in rats, mice but not teratogenic. Case reports of maternal, fetal deaths after use of podophyllin resin in pregnancy; no clear increase in birth defects with first-trimester exposure.	Because alternative treatments for genital warts in pregnancy are available, use not recommended; inadvertent use in early pregnancy is not indication for abortion.
Posaconazole	C	Embryotoxic in rabbits; teratogenic in rats at similar to human exposures. No experience in human pregnancy.	Not recommended

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 7 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Prednisone	B	Dose-dependent increased risk of cleft palate in mice, rabbits, hamsters; dose-dependent increase in genital anomalies in mice. Human data inconsistent regarding increased risk of cleft palate. Risk of growth retardation, low birth weight may be increased with chronic use; monitor for hyperglycemia with use in third trimester.	Adjunctive therapy for severe PCP; multiple other non-HIV-related indications
Primaquine	C	No animal data. Limited experience with use in human pregnancy; theoretical risk for hemolytic anemia if fetus has G6PD deficiency.	Alternate therapy for PCP, chloroquine-resistant malaria
Proguanil	C	Not teratogenic in animals. Widely used in malaria-endemic areas with no clear increase in adverse outcomes.	Alternate therapy and prophylaxis of *P. falciparum* malaria
Pyrazinamide	C	Not teratogenic in rats, mice. Limited experience with use in human pregnancy.	Active TB
Pyrimethamine	C	Teratogenic in mice, rats, hamsters (cleft palate, neural tube defects, and limb anomalies). Limited human data have not suggested an increased risk of birth defects; because folate antagonist, use with leucovorin.	Treatment and secondary prophylaxis of toxoplasmic encephalitis; alternate treatment of PCP
Quinidine gluconate	C	Generally considered safe in pregnancy; high doses associated with preterm labor. One case of fetal 8th nerve damage reported.	Alternate treatment of malaria, control of fetal arrhythmias
Quinine sulfate	C	High doses, often taken as an abortifacient, have been associated with birth defects, especially deafness, in humans and animals. Therapeutic doses have not been associated with an increased risk of defects in humans or animals. Monitor for hypoglycemia.	Treatment of chloroquine-resistant malaria
Ribavirin	X	Dose-dependent risk of multiple defects (craniofacial, central nervous system, skeletal, anophthalmia) in rats, mice, hamsters starting at below human doses. Reports of treatment during second half of pregnancy in nine women without incident; first 49 cases in registry did not suggest increased risk, but limited data.	Contraindicated in early pregnancy; no clear indications in pregnancy. Report exposures during pregnancy to Ribavirin Pregnancy Registry at (800) 593-2214 or www.ribavirinpregnancyregistry.com
Rifabutin	B	Not teratogenic in rats and rabbits; no specific concerns for human pregnancy.	Treatment or prophylaxis of MAC, active TB
Rifampin	C	Teratogenic at high doses in mice (cleft palate) and rats (spina bifida) but not in rabbits. No clear teratogenicity in humans.	Active TB
Simeprevir	C	Decreased fetal weights and increased skeletal variants in mice at 4x human exposure. Increased deaths and decreased fetal and neonatal growth and developmental delay after *in utero* exposure in rats. No experience in human pregnancy.	Treatment of HCV currently generally not recommended in pregnancy.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 8 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Sinecatechin ointment	C	No evidence of teratogenicity in rats and rabbits after oral or intravaginal dosing. No experience in human pregnancy.	Not recommended based on lack of data.
Sofosbuvir	B	No evidence of teratogenicity in rats or rabbits. No experience in human pregnancy.	Treatment of HCV generally not indicated in pregnancy. Regimens including ribavirin and interferon are contraindicated in pregnancy.
Streptomycin	D	No teratogenicity in mice, rats, guinea pigs. Possible increased risk of deafness and VIII nerve damage; no evidence of other defects.	Alternate therapy for active TB
Sulfadiazine	B	Sulfonamides teratogenic in some animal studies. No clear teratogenicity in humans; potential for increased jaundice, kernicterus if used near delivery.	Secondary prophylaxis of toxoplasmic encephalitis
Telaprevir	B	Not teratogenic in mice, rats. No human pregnancy data.	Treatment of HCV currently generally not indicated in pregnancy.
Telbivudine	B	Not teratogenic in rats, rabbits. Limited experience in human pregnancy.	Not recommended because of limited data in pregnancy. Use as part of fully suppressive antiretroviral regimen with antiretroviral agents active against both HIV and hepatitis B. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Tenofovir	B	No evidence of birth defects in rats, rabbits, or monkeys at high doses; chronic administration in immature animals of multiple species at 6–50 times human doses has led to dose-specific bone changes ranging from decreased mineral density to severe osteomalacia and fractures. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown. No evidence of increased birth defects in nearly 2000 first-trimester exposures in women.	Component of fully suppressive antiretroviral regimen in pregnant women. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Trichloracetic acid, bichloracetic acid	Not rated	No studies. Used topically so no systemic absorption expected.	Topical therapy of non-cervical genital warts
Trifluridine	C	Not teratogenic in rats, rabbits. Minimal systemic absorption expected with topical ocular use.	Topical agent for treatment of ocular herpes infections
Trimethoprim-sulfamethoxazole	C	Teratogenic in rats and mice. Possible increase in congenital cardiac defects, facial clefts, neural tube and urinary defects with first-trimester use. Unclear if higher levels of folate supplementation lower risk. Theoretical risk of elevated bilirubin in the neonate if used near delivery.	Therapy of PCP during pregnancy. Primary and secondary PCP prophylaxis in the second/third trimester; consider aerosolized pentamidine in first trimester. Recommend fetal ultrasound at 18–20 weeks after first-trimester exposure.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 9 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Valacyclovir	B	Not teratogenic in mice, rats, and rabbits. Experience with valacyclovir in pregnancy limited; prodrug of acyclovir, which is considered safe for use in pregnancy.	Treatment of HSV and varicella infections in pregnancy
Vancomycin	C	Not teratogenic in rats, rabbits. Limited human experience.	Serious bacterial infections
Voriconazole	D	Embryotoxic in rats, rabbits. Teratogenic in rats (cleft palate, hydronephrosis, and ossification defects). No experience with human use.	Not recommended

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; CMV = cytomegalovirus; CNS = central nervous system; FDA = Food and Drug Administration; G6PD = Glucose-6-phosphate dehydrogenase; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; TB = tuberculosis; VIII nerve = vestibulocochlear nerve; WHO = World Health Organization

Figure 1 (Last updated May 7, 2013; last reviewed May 7, 2013)

Immunization Schedule for Human Immunodeficiency Virus (HIV)-Infected Adults

VACCINE ▼ INDICATION ►	HIV infection CD4+ T lymphocyte count < 200 cells/μL	HIV infection CD4+ T lymphocyte count ≥ 200 cells/μL
Influenza *	1 dose IIV † annually	
Tetanus, diphtheria, pertussis (Td/Tdap) *	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs	
Varicella *	Contraindicated	2 doses
Human papillomavirus (HPV) Female *	3 doses through age 26 yrs	
Human papillomavirus (HPV) Male *	3 doses through age 26 yrs	
Zoster	Contraindicated	
Measles, mumps, rubella (MMR) *	Contraindicated	1 or 2 doses
Pneumococcal polysaccharide (PPSV23)	1 dose followed by a booster at 5 years	
Pneumococcal 13-valent conjugate (PCV13) *	1 dose	
Meningococcal *	1 or more doses	
Hepatitis A *	2 doses	
Hepatitis B *	3 doses	

*Covered by the Vaccine Injury Compensation Program

† IIV - Inactivated Influenza Vaccine. LAIV (live attenuated influenza vaccine) is not recommended for HIV-infected persons.

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection;
zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

Adapted from the Advisory Committee on Immunization Practices (ACIP) 2013 Adult Immunization Schedule. A summary of the adult immunization schedule vaccines and their primary indications, adverse events and contraindications can be found at: www.cdc.gov/vaccines/schedules/downloads/adult/mmwr-adult-schedule.pdf. For more detailed information on immunization of persons with HIV infection against influenza, pneumoccocal disease, hepatitis B, human papillomavirus, varicella, and hepatitis A, see disease-specific sections in the text and in Table 1. For additional information on these and other vaccines (tetanus, diphtheria, pertussis, measles, mumps, rubella, and meningococcal disease), refer to recommendations of the ACIP at: www.cdc.gov/vaccines/pubs/acip-list.htm.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Appendix A. Recommendations to Help HIV-infected Patients Avoid Exposure to, or Infection from, Opportunistic Pathogens

(Last updated May 7, 2013; last reviewed May 7, 2013)

Sexual Exposures

Male latex condoms, when used consistently and correctly during every act of sexual intercourse, are highly effective in preventing the sexual transmission of HIV and can reduce the risk for acquiring other sexually transmitted diseases (STDs), including chlamydia, gonorrhea, and trichomoniasis (http://www.cdc.gov/condomeffectiveness/latex.htm). Correct and consistent use of male latex condoms not only reduces the risk of HIV transmission but might reduce the risk for transmission of herpes simplex virus, syphilis, and chancroid when the infected area or potential site of exposure is covered, although data for this effect are more limited.[1,2] Male condoms also appear to reduce the risk for human papillomavirus associated diseases (i.e., genital warts, cervical cancer) and thereby mitigate the adverse consequences of infection with HPV. Although data for female condoms are limited, women should consider using them to prevent the acquisition of STDs and reduce their risk of transmitting HIV.[3] Spermicides containing nonoxynol-9 are not effective for HIV/STD prevention[4-6] and may increase risk of transmission to uninfected partners;[7,8] nonoxynol-9 **should not be used** as a microbicide or lubricant during vaginal or anal intercourse.

As with many non-sexually transmitted opportunistic infections, intercurrent infections with sexually transmitted pathogens (especially pathogens that cause genital ulcers such as herpes simplex, syphilis, and chancroid) can, if untreated, stimulate increases in HIV viral load and consequent declines in CD4 T lymphocyte (CD4) count.[9] Furthermore, acquisition of STDs by HIV-infected patients indicates participation in high-risk sexual behavior that is capable of transmitting HIV to others, the risk for which is substantially increased in the presence of genital tract inflammation (e.g., from gonorrhea or chlamydia) and genital ulcer disease (e.g., herpes simplex virus-2 infection, syphilis).[9-14] All HIV-infected persons, including those who are asymptomatic, should be tested at initial evaluation for trichomoniasis in women; syphilis, urogenital gonorrhea, and chlamydia in men and women; and oral gonorrhea, rectal gonorrhea, and rectal chlamydia for male patients reporting receptive sex at these anatomic sites.[15-17] Nucleic acid amplification testing methods are the most sensitive and specific method for the diagnosis of anogenital, oral, and rectal chlamydia and gonorrhea infection. Detailed recommendations for specific testing in HIV-infected persons can be found at the following site: http://www.cdc.gov/std/treatment. For all sexually active patients, screening should be repeated at least annually and more frequently depending on individual risk or symptoms. In addition to identifying and treating STDs, providers should communicate prevention messages, discuss sexual and drug-use behaviors, positively reinforce safer behaviors, refer patients for services such as substance abuse treatment, and facilitate partner notification, counseling, and testing.

Specific sex practices should be avoided that might result in oral exposure to feces (e.g., oral-anal contact) to reduce the risk for intestinal infections (e.g., cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, lymphogranuloma venereum [LGV] serovars of *C. trachomatis*, hepatitis A [HAV]). Persons who wish to reduce their risk for exposure might consider using dental dams or similar barrier methods for oral-anal and oral-genital contact, changing condoms after anal intercourse, and wearing latex gloves during digital-anal contact. Frequent washing of hands and genitals with warm soapy water during and after activities that might bring these body parts in contact with feces might further reduce risk for illness.

Sexual transmission of hepatitis C virus (HCV) and infection can occur, especially among HIV-infected men who have sex with men (MSM).[18-20] HIV-infected MSM not known to be infected with HCV, and who present with new and unexplained increases in alanine aminotransferase, should be tested for HCV virus infection. Routine (e.g., annual) HCV testing should be considered for MSM with high risk sexual behaviors or with a diagnosis of an ulcerative STD.[16]

HAV can be transmitted sexually, therefore vaccination is recommended for all susceptible MSM, as well as

others with indications for HAV vaccination (e.g., injection-drug users, persons with chronic liver disease or who are infected with hepatitis B [HBV]). HAV vaccination is also recommended for other HIV-infected persons (e.g., injection-drug users, persons with chronic liver disease or who are infected with HBV or HCV). HBV vaccination is recommended for all susceptible HIV-infected patients. HBV infection can occur when mucous membranes are exposed to blood or body fluids that contain blood, which might occur during some types of sexual contact. HIV-infected patients coinfected with HBV or HCV should be reminded that use of latex condoms not only reduces their risk of transmitting HIV to sexual partners but reduces their risk of transmitting these viral hepatitis infections as well.

Injection-Drug-Use Exposures

Injection-drug use is a complex behavior that puts HIV-infected persons at risk for HBV and HCV infection, additional possibly drug-resistant strains of HIV, and other bloodborne pathogens. Providers should assess a person's readiness to change this practice and encourage activities to provide education and support directed at recovery. Patients should be counseled to stop using injection drugs and to enter and complete substance abuse treatment, including relapse prevention programs.[21]

For patients who continue to inject drugs, health-care providers should advise them to adhere to the following practices:

- Never reuse or share syringes, needles, water, or drug-preparation equipment; if injection equipment that has been used by other persons is shared, the implements should first be cleaned with bleach and water before use.
- Use only sterile syringes and needles obtained from a reliable source (e.g., pharmacies or syringe-exchange programs).
- Use sterile (e.g., boiled) water to prepare drugs, and if this is not feasible, use clean water from a reliable source (e.g., fresh tap water); use a new or disinfected container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs.
- Clean the injection site with a new alcohol swab before injection.
- Safely dispose of syringes and needles after one use.

All susceptible injection-drug–users should be vaccinated against HBV and HAV infection. HIV-infected injection drug users not known to be HCV infected who present with new and unexplained increases in alanine aminotransferase should be tested for HCV infection. Routine (e.g., annual) HCV testing should be considered for injection drug users who continue to inject drugs.

Environmental and Occupational Exposures

Certain activities or types of employment might increase the risk for exposure to tuberculosis (TB). These include residency or occupation in correctional institutions and shelters for the homeless, other settings identified as high risk by local health authorities, as well as volunteer work or employment in health-care facilities where patients with TB are treated. Decisions regarding the risk of occupational exposure to TB should be made in conjunction with a health-care provider and should be based on such factors as the patient's specific duties in the workplace, the prevalence of TB in the community, and the degree to which precautions designed to prevent the transmission of TB are taken in the workplace. These decisions will affect the frequency with which the patient should be screened for TB.

Day care providers and parents of children in child care are at increased risk for acquiring cytomegalovirus infection, cryptosporidiosis, and other infections (e.g., HAV, giardiasis) from children. The risk for acquiring infection can be diminished by practicing optimal hygienic practices (e.g., washing hands with soap and water, or alcohol-based hand sanitizers if soap and water are unavailable) after fecal contact (e.g., during

diaper changing) and after contact with urine or saliva.

Occupations involving contact with animals (e.g., veterinary work and employment in pet stores, farms, or slaughterhouses) might pose a risk for toxoplasmosis, cryptosporidiosis, salmonellosis, campylobacteriosis, *Bartonella* infection, *E. coli* infection, and other infections of concern to any immunocompromised host (e.g., leptospirosis, brucellosis, *Capnocytophaga spp*.). However, available data are insufficient to justify a recommendation against HIV-infected persons working in such settings. Wearing gloves and good hand hygiene can reduce the risk of infection.

Contact with young farm animals, specifically animals with diarrhea, should be avoided to reduce the risk for cryptosporidiosis. Since soils and sands can be contaminated with *Toxoplasma gondii* and *Cryptosporidium parvum*, persons who have extended contact with these materials (e.g., gardening; playing in or cleaning sandboxes) should wash their hands thoroughly with soap and water following exposure. In areas where histoplasmosis is endemic, patients should avoid activities known to be associated with increased risk (e.g., creating dust when working with surface soil; cleaning chicken coops that are heavily contaminated with compost droppings; disturbing soil beneath bird-roosting sites; cleaning, remodeling or demolishing old buildings; and cave exploring). In areas where coccidioidomycosis is endemic, when possible, patients should avoid activities associated with increased risk, including extensive exposure to disturbed native soil (e.g., building excavation sites, during dust storms).

Pet-Related Exposures

Health-care providers should advise HIV-infected persons of the potential risk posed by pet ownership. However, they should be sensitive to the psychological benefits of pet ownership and should **not** routinely advise HIV-infected persons to part with their pets. Specifically, providers should advise HIV-infected patients of the following precautions.

General

HIV-infected persons should avoid direct contact with stool from pets or stray animals. Veterinary care should be sought when a pet develops diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea.

When obtaining a new pet, HIV-infected patients should avoid animals aged <6 months (or <1 year for cats) and specifically animals with diarrhea. Because the hygienic and sanitary conditions in pet-breeding facilities, pet stores, and animal shelters vary, patients should be cautious when obtaining pets from these sources. Stray animals should also be avoided, and specifically those with diarrhea.

Gloves should always be worn when handling feces or cleaning areas that might have been contaminated by feces from pets. Patients should wash their hands after handling pets and also before eating. Patients, especially those with CD4 cell counts < 200 cells/μL should avoid direct contact with all animal feces to reduce the risk for toxoplasmosis, cryptosporidiosis, salmonellosis, campylobacteriosis, *E. coli* infection, and other infectious illnesses. HIV-infected persons should limit or avoid direct exposure to calves and lambs (e.g., farms, petting zoos). Paying attention to hand hygiene (i.e., washing hands with soap and water, or alcohol-based hand sanitizers if soap and water are unavailable) and avoiding direct contact with stool are important when visiting premises where these animals are housed or exhibited.

Patients should not allow pets, particularly cats, to lick patients' open cuts or wounds and should take care to avoid any animal bites. Patients should wash all animal bites, animal scratches, or wounds licked by animals promptly with soap and water and seek medical attention. A course of antimicrobial therapy might be recommended if the wounds are moderate or severe, demonstrate crush injury and edema, involve the bones of a joint, involve a puncture of the skin near a joint, or involve a puncture of a joint directly.

Cats

Patients should be aware that cat ownership may under some circumstances increase their risk for toxoplasmosis and *Bartonella* infection, and enteric infections. Patients who elect to obtain a cat should adopt or purchase an animal aged >1 year and in good health to reduce the risk for cryptosporidiosis, *Bartonella* infection, salmonellosis, campylobacteriosis, and *E. coli* infection.

Litter boxes should be cleaned daily, preferably by an HIV-negative, non-pregnant person; if HIV-infected patients perform this task, they should wear gloves and wash their hands thoroughly afterward to reduce the risk for toxoplasmosis. To further reduce the risk for toxoplasmosis, HIV-infected patients should keep cats indoors, not allow them to hunt, and not feed them raw or undercooked meat. Although declawing is not usually advised, patients should avoid activities that might result in cat scratches or bites to reduce the risk for *Bartonella* infection. Patients should also wash sites of cat scratches or bites promptly and should not allow cats to lick patients' open cuts or wounds. Care of cats should include flea control to reduce the risk for *Bartonella* infection. Testing cats for toxoplasmosis or *Bartonella* infection **is not recommended**, as such tests cannot accurately identify animals that pose a current risk for human infection.

Birds

Screening healthy birds for *Cryptococcus neoformans*, *Mycobacterium avium*, or *Histoplasma capsulatum* **is not recommended**.

Other

HIV-infected persons should avoid or limit contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) and chicks and ducklings because of the high risk for exposure to *Salmonella spp*. Gloves should be used during aquarium cleaning to reduce the risk for infection with *Mycobacterium marinum*. Contact with exotic pets (e.g., nonhuman primates) should be avoided.

Food- and Water-Related Exposures

Food

Contaminated food is a common source of enteric infections. Transmission most often occurs by ingestion of undercooked foods or by cross-contamination of foods in the kitchen.

Health-care providers should advise HIV-infected persons, particularly those with a CD4 count <200 cells/μL, not to eat raw or undercooked eggs, including specific foods that might contain raw eggs (e.g., certain preparation of Hollandaise sauce, Caesar salad dressings, homemade mayonnaises, uncooked cookie and cake batter, eggnog); raw or undercooked poultry, meat, and seafood (raw shellfish in particular); unpasteurized dairy products (including milk and cheese); unpasteurized fruit juices; and raw seed sprouts (e.g., alfalfa sprouts or mung bean sprouts).

Meat and poultry are safest when adequate cooking is confirmed by thermometer. Current U.S. Department of Agriculture (USDA) guidance (http://www.fsis.usda.gov/Factsheets/Keep_Food_Safe_Food_Safety_Basics/index.asp) is that the internal temperature be at least 145°F (63°C) for whole cuts of meat, 160°F (71°C) for ground meat excluding poultry, and 165°F (74°C) for poultry; whole cuts of meat and poultry should rest at least three minutes before carving and consuming. Immunocompromised persons who wish to maximally ensure their cooked meats are safe to eat may choose to use the following recommendations: the internal temperature should be at least 165°F (74°C) for all types of red meats and 180°F (82°C) for poultry. If a thermometer is not used when cooking meats, the risk for illness is decreased by eating poultry and meat that have no trace of pink color. However, color change of the meat (e.g., absence of pink) does not always correlate with internal temperature. Irradiated meats, if available, are predicted to eliminate the risk of foodborne enteric infection. Use of microwaves as a primary means of cooking of potentially contaminated foods (e.g., meats, hot dogs) should be avoided because microwave cooking is not uniform.

Produce items should be washed thoroughly; providers may wish to advise patients that produce is safest when cooked.

Health-care providers should advise HIV-infected persons to avoid cross-contamination of foods. Salad preparation prior to handling of raw meats or other uncooked, potentially contaminated foods decreases risk. Uncooked meats, including hot dogs, and their juices should not come into contact with other foods. Hands, cutting boards, counters, knives, and other utensils should be washed thoroughly (preferably in a dish washer on hot cycle) after contact with uncooked foods.

Soft cheeses (e.g., feta, Brie, Camembert, blue-veined, and Mexican-style cheese such as queso fresco) and prepared deli foods (including coldcuts, salads, hummus, hot dogs, pâtés) are potential sources of *Listeria monocytogenes* infection, which can lead to serious, even fatal, systemic infection in HIV-infected patients with low CD4 cell counts; consumption of these foods should be avoided.

Hard cheeses, processed cheeses, cream cheese, including slices and spreads; cottage cheese or yogurt; and canned or shelf-stable pâté and meat spreads need not be avoided. Avoid raw or unpasteurized milk, including goat's milk, or foods that contain unpasteurized milk or milk products.

Additional and more detailed information on the safe handling and preparation of food for persons with HIV infection can be found through the websites of the Food and Drug Administration (http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm135844.htm) and the USDA (http://www.fsis.usda.gov/pdf/food_safety_for_people_with_hiv.pdf).

Water

Patients should **not** drink water directly from lakes or rivers because of the risk for cryptosporidiosis, giardiasis, and toxoplasmosis. Waterborne infection can also result from swallowing water during recreational activities. All HIV-infected patients should avoid swimming in water that is probably contaminated with human or animal waste and should avoid swallowing water during swimming. Patients, especially those with CD4 cell counts <200 cells/μL, should also be made aware that swimming or playing in lakes, rivers, and oceans as well as some swimming pools, recreational water parks, and ornamental water fountains can expose them to enteric pathogens (e.g., *Cryptosporidium*, *Giardia*, norovirus, Shiga toxin-producing *E. coli*) that cause diarrheal illness and to which their HIV infection makes them more susceptible.

Outbreaks of diarrheal illness have been linked to drinking water from municipal water supplies. During outbreaks or in other situations in which a community boil-water advisory is issued, boiling water for >1 minute will eliminate the risk for most viral, bacterial, and parasitic causes of diarrhea, including cryptosporidiosis. Using submicron, personal-use water filters (home/office types) or drinking bottled water might also reduce the risk from municipal and from well water.

Available data are inadequate to support a recommendation that all HIV-infected persons boil or otherwise avoid drinking tap water in non-outbreak settings. However, persons who wish to take independent action to reduce their risk for waterborne cryptosporidiosis might take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with a health-care provider. Persons who choose to use a personal-use filter or bottled water should be aware of the complexities involved in selecting the appropriate products, the lack of enforceable standards for destruction or removal of oocysts, product cost, and the difficulty of using these products consistently.

Patients taking precautions to avoid acquiring pathogens from drinking water should be advised that ice made from contaminated tap water also can be a source of infection. Patients should also be made aware that fountain beverages served in restaurants, bars, theaters, and other public places also might pose a risk, because these beverages, and the ice they might contain, are usually made from tap water. Nationally distributed brands of bottled or canned water and carbonated soft drinks are safe to drink. Commercially packaged (i.e., sealed at the factory and unopened), non-carbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those that can be stored unrefrigerated on grocery

shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by users with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time they are consumed might be either fresh (i.e., unpasteurized) or heat treated (i.e., pasteurized); only juices labeled as pasteurized should be considered safe to consume. Other pasteurized beverages and beers also are considered safe.

Travel-Related Exposures

HIV-infected travelers to developing countries, especially travelers who are severely immunosuppressed, risk exposure to both opportunistic and non-opportunistic pathogens not prevalent in the United States. Health-care providers or specialists in travel medicine (a list can be found at http://www.istm.com) should be consulted 4 to 6 weeks in advance of travel to fully review and implement all measures necessary to prevent illness abroad. The Centers for Disease Control and Prevention (CDC) maintain a website accessible to travelers and their care providers at http://www.cdc.gov/travel and regularly publishes recommendations for prevention of disease while traveling in the CDC's Yellow Book (Health Information for International Travel).[22] The CDC's travel website allows users to locate prevention recommendations according to geographic destination and to find updates on international disease outbreaks that might pose a health threat to travelers. A detailed review of concerns faced by immunocompromised persons traveling abroad is available at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers.htm in the Yellow Book.

The following summary advice should be considered for all HIV-infected travelers but does substitute for destination-specific consultation with a travel medicine specialist.

The risk for foodborne and waterborne infections among HIV-infected persons is magnified during travel to economically developing countries. Travelers to such countries may wish to additionally consult the section *Food- and Water-Related Exposures*, above, as well as recommendations for food and water precautions and water disinfection in the CDC Yellow Book (Health Information for Travelers).[22] Specifically, persons who travel to economically developing areas should avoid foods and beverages that might be contaminated, as well as tap water, ice made with tap water, and items sold by street vendors. Raw fruits or vegetables that might have been washed in tap water should be avoided. Foods and beverages that are usually safe include steaming hot foods, fruits that are peeled by the traveler, unopened and properly bottled (including carbonated) beverages, hot coffee and tea, beer, wine, and water that is brought to a rolling boil for 1 minute. Treating water with iodine or chlorine can be as effective as boiling for preventing infections with most pathogens. Iodine and chlorine treatments may not prevent infection with *Cryptosporidium*; however these treatments can be used when boiling is not practical.

Waterborne infections might result from swallowing water during recreational activities. To reduce the risk for parasitic (e.g., cryptosporidiosis, giardiasis, toxoplasmosis) and bacterial infections, patients should avoid swallowing water during swimming and should not swim in water that might be contaminated (e.g., with sewage or animal waste). HIV-infected persons traveling to developing countries should also be advised to **not** use tap water to brush their teeth.

Scrupulous attention to safe food and water consumption and good hygiene (i.e., regularly washing hands with soap and water, or alcohol-based hand sanitizers if soap and water are unavailable) are the most effective methods for reducing risk of travelers' diarrhea. Antimicrobial prophylaxis for travelers' diarrhea **is not recommended** routinely for HIV-infected persons traveling to developing countries. Such preventive therapy can have adverse effects, can promote the emergence of drug-resistant organisms, and can increase the risk of *C. difficile*-associated diarrhea. Nonetheless, studies (none involving an HIV-infected population) have reported that prophylaxis can reduce the risk for diarrhea among travelers. Under selected circumstances (e.g., those in which the risk for infection is high and the period of travel brief), the health-care provider and patient might weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted.

HIV-infected travelers to developing countries should consider carrying a sufficient supply of an antimicrobial agent to be taken empirically if diarrhea occurs. Antimicrobial resistance among enteric bacterial pathogens outside the United States is a growing public health problem; therefore, the choice of antibiotic should be made in consultation with a clinician based on the traveler's destination. Travelers should consult a physician if they develop severe diarrhea that does not respond to empirical therapy, if their stools contain blood, they develop fever with shaking chills, or dehydration occurs. Antiperistaltic agents (e.g., diphenoxylate and loperamide) are used for treating diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist for more than 48 hours.

Live-virus vaccines should, in general, **not** be used. An exception is measles vaccine, which is recommended for non-immune persons. However, measles vaccine **is not recommended** for persons who are severely immunosuppressed. Severely immunosuppressed persons who must travel to measles-endemic countries should consult a travel medicine specialist regarding possible utility of prophylaxis with immune globulin. Another exception is varicella vaccine, which can be administered to asymptomatic susceptible persons with a CD4 cell count ≥200 cells/μL. For adults and adolescents with CD4 cell counts <200 cells/μL, varicella-zoster immune globulin (VariZIG™) is indicated after close contact with a person who has active varicella or zoster and anti-herpetic antiviral therapy (e.g., acyclovir, famciclovir, valacyclovir) is recommended in the event vaccination or exposure results in clinical disease (for further details, see Varicella-Zoster Virus Diseases chapter). Persons at risk for and non-immune to polio and typhoid fever or who require influenza vaccination should be administered only inactivated formulations of these vaccines **not** live-attenuated preparations.

Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy among HIV-infected persons. Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered vaccination. If travel to a zone with yellow fever is necessary and vaccination is not administered, patients should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided a vaccination waiver letter. Preparation for travel should include a review and updating of routine vaccinations, including diphtheria, tetanus, acellular pertussis, and influenza.

Killed and recombinant vaccines (e.g., influenza, diphtheria, tetanus, rabies, HAV, HBV, Japanese encephalitis, meningococcal vaccines) should usually be used for HIV-infected persons just as they would be used for non-HIV–infected persons anticipating travel. Comprehensive and regularly updated information regarding recommended vaccinations and recommendations when a vaccination is contraindicated are listed by vaccine at http://www.cdc.gov/vaccines/pubs/acip-list.htm.

References

1. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. Jul 13 2009;169(13):1233-1240. Available at http://www.ncbi.nlm.nih.gov/pubmed/19597073.
2. Koss CA, Dunne EF, Warner L. A systematic review of epidemiologic studies assessing condom use and risk of syphilis. *Sex Transm Dis*. Jul 2009;36(7):401-405. Available at http://www.ncbi.nlm.nih.gov/pubmed/19455075.
3. Minnis AM, Padian NS. Effectiveness of female controlled barrier methods in preventing sexually transmitted infections and HIV: current evidence and future research directions. *Sex Transm Infect*. Jun 2005;81(3):193-200. Available at http://www.ncbi.nlm.nih.gov/pubmed/15923284.
4. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Weir SS, Wong EL. A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med*. Aug 20 1998;339(8):504-510. Available at http://www.ncbi.nlm.nih.gov/pubmed/9709043.
5. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Tweedy KG. Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydial infection: a randomized controlled trial. *JAMA*. Mar 6 2002;287(9):1117-1122. Available at http://www.ncbi.nlm.nih.gov/pubmed/11879108.
6. Richardson BA, Lavreys L, Martin HL, Jr., et al. Evaluation of a low-dose nonoxynol-9 gel for the prevention of sexually transmitted diseases: a randomized clinical trial. *Sex Transm Dis*. Jul 2001;28(7):394-400. Available at

http://www.ncbi.nlm.nih.gov/pubmed/11460023.

7. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet*. Sep 28 2002;360(9338):971-977. Available at http://www.ncbi.nlm.nih.gov/pubmed/12383665.
8. Phillips DM, Taylor CL, Zacharopoulos VR, Maguire RA. Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium. *Contraception*. Sep 2000;62(3):149-154. Available at http://www.ncbi.nlm.nih.gov/pubmed/11124363.
9. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. Jul 2010;10(7):455-463. Available at http://www.ncbi.nlm.nih.gov/pubmed/20610327.
10. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. Feb 1999;75(1):3-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/10448335.
11. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. Oct 2001;28(10):579-597. Available at http://www.ncbi.nlm.nih.gov/pubmed/11689757.
12. McClelland RS, Wang CC, Mandaliya K, et al. Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. *AIDS*. Jan 5 2001;15(1):105-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/11192850.
13. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. *Lancet*. Jun 28 1997;349(9069):1868-1873. Available at http://www.ncbi.nlm.nih.gov/pubmed/9217758.
14. Ghys PD, Fransen K, Diallo MO, et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS*. Oct 1997;11(12):F85-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/9342059.
15. Centers for Disease C, Prevention, Health R, Services A, National Institutes of H, America HIVMAotIDSo. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. Jul 18 2003;52(RR-12):1-24. Available at http://www.ncbi.nlm.nih.gov/pubmed/12875251.
16. Workowski KA, Berman S, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160459.
17. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Sep 1 2009;49(5):651-681. Available at http://www.ncbi.nlm.nih.gov/pubmed/19640227.
18. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS*. May 11 2007;21(8):983-991. Available at http://www.ncbi.nlm.nih.gov/pubmed/17457092.
19. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS*. Jul 31 2009;23(12):F1-7. Available at http://www.ncbi.nlm.nih.gov/pubmed/19542864.
20. Centers for Disease C, Prevention. Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. *MMWR Morb Mortal Wkly Rep*. Jul 22 2011;60(28):945-950. Available at http://www.ncbi.nlm.nih.gov/pubmed/21775948.
21. CDC. HIV prevention bulletin: medical advice for persons who inject illicit drugs - May 9, 1997.
22. Centers for Disease C, Prevention. *CDC Health Information for International Travel, 2012*. Atlanta, GA: US Department of Heath and Human Services, Public Health Service; 2012.

Appendix B. List of Abbreviations (Last updated May 7, 2013; last reviewed May 7, 2013)

Acronym/Abbreviation	Definition
ABGs	arterial blood gasses
ACTG	AIDS Clinical Trials Group
AFB	acid-fact bacilli
AIN	anal intraepithelial neoplasia
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
ARV	antiretroviral
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	atypical squamous cells—cannot exclude high grade cervical squamous intraepithelial lesion
ASC-US	atypical squamous cells of uncertain significance
AST	serum aspartate aminotransferase
AUC	area under the curve
BA	bacillary angiomatosis
BAL	bronchoalveolar lavage
BID	twice a day
BIW	twice a week
CAP	community-acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CD4	CD4 T lymphocyte cell
CDC	the Centers for Disease Control and Prevention
CDI	*Clostridium difficile*-associated infection
CES-D	Center for Epidemiologic Studies Depression Scale
CFU	colony-forming unit
CIA	chemiluminescence immunoassays
CIN	cervical intraepithelial neoplasia
C_{max}	maximum concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CNS	central nervous system
CPE	central nervous system penetration effectiveness
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CT	computed tomography

CYP3A4	Cytochrome P450 3A4
DAAs	direct acting antiviral agents
DOT	directly observed therapy
DS	double strength
EDTA	ethylenediaminetetraacetic acid
EIAs	enzyme immunoassays
EM	erythema multiforme
FDA	Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorbed
g	gram
G6PD	Glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HPA	hypothalamic-pituitary-adrenal
HPV	human papillomavirus
HSIL	high grade cervical squamous intraepithelial lesion
HSV	herpes simplex virus
HSV-1	herpes simplex virus 1
HSV-2	herpes simplex virus 2
ICP	intracranial pressure
ICU	intensive care unit
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assays
IM	intramuscular
IND	investigational new drug
IRIS	immune reconstitution inflammatory syndrome
IRU	immune recovery uveitis
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	JC virus
KS	Kaposi Sarcoma
LEEP	loop electrosurgical excision procedure
LP	lumbar puncture
LSIL	low grade squamous intraepithelial lesion

LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium intracellulare*
MCD	multicentric Castleman's disease
MDR TB	multi-drug-resistant tuberculosis
mg	milligram
mmHg	millimeters of mercury
MSM	men who have sex with men
MTB	*Mycobacterium tuberculosis*
NAA	nucleic acid amplification
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OI	opportunistic infection
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PEL	primary effusion lymphoma
PK	pharmacokinetic
PML	progressive multifocal Leukoencephalopathy
PO	orally
PORN	Progressive Outer Retinal Necrosis
PPV	polysaccharide vaccine
PSI	pneumonia severity index
q(n)h	every "n" hours
qAM	every morning
QID	four times a day
qPM	every evening
RPR	rapid plasma reagin
RVR	rapid virological response
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SQ	subcutaneous
SS	single strength
STD	sexually transmitted disease
SVR	sustained virologic response
TB	tuberculosis
TDM	therapeutic drug monitoring
TE	*Toxoplasma* encephalitis

TEN	toxic epidermal necrolysis
TID	three times daily
TIW	three times weekly
TP-PA	*T. pallidum* particle agglutination
TST	tuberculin skin test
ULN	upper limit of normal
VAIN	vaginal intra-epithelial neoplasia
VDRL	Venereal Disease Research Laboratory
VIII nerve	vestibulocochlear nerve
VIN	vulvar intraepithelial neoplasia
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

Abbreviation	**Drug Name**
3TC	lamivudine
5-FU	fluorouracil
ATV/r	ritonavir-boosted atazanavir
BCA	bichloroacetic acid
BOC	boceprevir
COBI	cobicistat
ddA-TP	dideoxyadenosine triphosphate
ddI	didanosine
DHA	dihydroartemisinin
EFV	efavirenz
EMB	ethambutol
EVG	elvitegravir
FTC	emtricitabine
INH	isoniazid
MVC	maraviroc
PCV13	13-valent pneumococcal conjugate vaccine
PegIFN	peginterferon alfa
PI	protease inhibitor
PPV23	23-valent pneumococcal polysaccharides vaccine
PZA	pyrazinamide
RAL	raltegravir
RBV	ribavirin
RFB	rifabutin
RIF	rifampin

RPT	rifapentine
SMX	sulfamethoxazole
TCA	trichloroacetic acid
TDF	tenofovir disoproxil fumarate
TMP	trimethoprim
TMP-SMX	trimethoprim-sulfamethoxazole
TVR	telaprevir
ZDV	zidovudine

Appendix C. Panel Roster and Financial Disclosures

Leadership (Last Reviewed: February 1, 2016; Last Updated: February 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Benson, Constance	*University of California, San Diego*	None	N/A
Brooks, John T.	*Centers for Disease Control and Prevention*	None	N/A
Holmes, King	*University of Washington School of Medicine*	None	N/A
Kaplan, Jonathan*	*Centers for Disease Control and Prevention*	None	N/A
Masur, Henry	*National Institutes of Health*	None	N/A
Pau, Alice	*National Institutes of Health*	None	N/A

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from March 1, 2014, through March 1, 2016.

* Retired from the panel in March, 2016

Pneumocystis Pneumonia (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Crothers, Kristina	*Yale University School of Medicine*	• NIH	• Research
Furrer, Hansjakob	*Universitatsspital Bern, Switzerland*	None	N/A
Helweg-Larsen, Jannik	*Rigshospitalet, Copenhagen University, Denmark*	None	N/A
Huang, Laurence	*University of California, San Francisco*	• NIH	• Research
Kovacs, Joe*	*National Institutes of Health*	None	N/A
Miller, Robert	*University College London, England*	• Gilead	• Honoraria, Speaker's Bureau
		• Janssen-Cilag	• Honoraria, Speaker's Bureau
		• Mark Allen Healthcare	• Honoraria
		• Merck	• Honoraria, Speaker's Bureau
Morris, Alison	*University of Pittsburgh Medical School*	• Associates of Cape Cod	• Research Support
		• Gilead	• Research Support
		• NIH	• Research Support
		• Roche	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Toxoplasma gondii Encephalitis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Boyd, Sarita	*Food and Drug Administration*	None	N/A
Chow, Felicia	*University of California, San Francisco*	• Gilead	• Stock Holder†
Kovacs, Joe*	*National Institutes of Health*	None	N/A
Lai, Leon	*Washington Hospital Center*	• Advanced Medical	• Stock Holder
		• Amgen	• Stock Holder
		• Bristol-Myers Squibb	• Stock Holder
		• DuPont	• Stock Holder
		• Eli Lilly & Co.	• Stock Holder
		• Merck	• Stock Holder
		• Pfizer	• Stock Holder
		• Schering-Plough	• Stock Holder
Miro, Jose M.	*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain*	• Abbvie	• Consultant, Honoraria, Speaker's Bureau
		• Astellas	• Consultant
		• Bristol-Myers Squibb	• Consultant, Honoraria, Research Support, Speaker's Bureau
		• Cubist	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Fundacion Maximo Soriano Jimenez, Barcelona, Spain	• Research Support
		• Gilead	• Consultant, Honoraria, Speaker's Bureau
		• GlaxoSmithKline	• Honoraria, Speaker's Bureau
		• Instituto de Salud Carlos III, Spanish Ministry of Health, Madrid, Spain	• Research Support
		• Janssen-Cilag	• Speaker's Bureau
		• Merck	• Consultant, Speaker's Bureau
		• National Institutes of Health	• Research Support
		• Novartis	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Pfizer	• Consultant, Speaker's Bureau
		• ViiV Healthcare	• Honoraria, Speaker's Bureau, Research Support

Toxoplasma gondii Encephalitis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Montoya, Jose	*Stanford University*	None	N/A
Podzamczer, Daniel	*Hospital Universitari de Bellvitge, Spain*	• Abbott	• Advisory Board, Speaker's Bureau
		• Boehringer Ingelheim	• Advisory Board, Research Support, Speaker's Bureau, Travel Support
		• Bristol-Myers Squibb	• Advisory Board, Speaker's Bureau
		• Gilead	• Advisory Board, Research Support, Speaker's Bureau
		• GlaxoSmithKline	• Advisory Board, Research Support, Speaker's Bureau
		• Janssen-Cilag	• Advisory Board, Speaker's Bureau
		• Merck	• Advisory Board, Speaker's Bureau
		• Pfizer	• Advisory Board, Research Support, Speaker's Bureau
		• ViiV	• Advisory Board, Research Support, Speaker's Bureau

* Group lead; † Divested

Note: Members were asked to disclose all relationships from 24 months prior to the update date. The period of reporting was from September 1, 2012, through September 1, 2014.

Cryptosporidiosis and Microsporidiosis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Desruisseaux, Mahalia	*Albert Einstein College of Medicine*	None	N/A
Didier, Elizabeth	*Tulane University*	None	N/A
Ward, Honorine	*Tufts University Medical School*	None	N/A
Weiss, Louis*	*Albert Einstein College of Medicine*	• NIH	• Research Support
White, A. Clinton	*University of Texas Medical Branch*	None	N/A
Xiao, Lihua	*Centers for Disease Control and Prevention*	• Water Research Foundation	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the update date. The period of reporting was from September 1, 2012, through September 1, 2014.

Mycobacterium tuberculosis Infection and Disease (Last Reviewed: September 1, 2014; Last Updated:September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Dooley, Kelly	*Johns Hopkins University*	• Viiv Health Care	• Research Support
Gandhi, Neel	*Rollins School of Public Health-Emory University*	None	N/A
Havlir, Diane*	*University of California, San Francisco*	• Abbot	• Research Support
		• Gilead	• Research Support
Luetkemeyer, Annie	*University of California, San Francisco*	• Cepheid	• Research Support
Maartens, Gary	*University of Cape Town, South Africa*	None	N/A
Meintjes, Graeme	*University of Cape Town, South Africa*	• Sanofi-Aventis	• Speaker's Bureau
Shah, Sarita	*Centers for Disease Control and Prevention*	None	N/A
Sterling, Timothy	*Vanderbilt University*	• Otsuka	• DSMB Member
		• Sanofi	• Consultant

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Disseminated *Mycobacterium avium* Complex Disease (Last Reviewed: November 1, 2012; Last Updated: November 1, 2012)

Member		Financial Disclosure	
		Company	Relationship
Cohn, David	*University of Colorado School of Medicine*	None	N/A
Currier, Judith	*University of California, Los Angeles*	• Achillion	• DSMB Member
		• EMD Seronon	• Advisory Board
		• Gilead	• Consultant
		• GlaxoSmithKline	• Honoraria
		• Janssen-Cilag	• Honoraria, Travel Support
		• Koronis	• DSMB Member
		• Merck	• Advisory Board, Research Support
		• Pfizer	• Advisory Board
		• Schering-Plough	• Research Support
		• Tibotec	• Advisory Support, Research Support, Travel Support
Dorman, Susan	*Johns Hopkins University*	• Bill and Melinda Gates Foundation	• Research Support
		• FDA	• Research Support
		• NIH	• Research Support
Gordin, Fred*	*Veterans Affairs Medical Center; Washington, DC*	None	N/A
Horsburgh, C. Robert	*Boston University*	• Bill and Melinda Gates Foundation	• Travel Support
		• CDC	• Research Support
		• Medical Research Council (UK)	• Travel Support
		• NIH	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months before the writing panel convened. The period of reporting was from June 1, 2008, through November 1, 2012.

Bacterial Respiratory Disease (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Crothers, Kristina*	*University of Washington*	None	N/A
Miller, Robert	*University College London, England*	• Gilead	• Honoraria, Speaker's Bureau
		• Mark Allen Healthcare	• Honoraria
		• Merck	• Honoraria, Speaker's Bureau
Moore, Matthew	*Centers for Disease Control and Prevention*	None	N/A
Morris, Alison	*University of Pittsburgh Medical School*	• Cape Cod Association	• Research Support
		• Gilead	• Research Support
		• NIH	• Research Support
		• Roche	• Research Support
Niederman, Michael	*Winthrop University Hospital*	• Bayer	• Advisory Board, Honoraria, Research Support
		• Cubist	• Research Support
		• Merck	• Advisory Board
		• Pfizer	• Advisory Board, Honoraria
		• Thermo-Fisher	• Honoraria

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012 through September 1, 2014.

Bacterial Enteric Infections (Last Reviewed: April 1, 2016; Last Updated: April 1, 2016)

Member		Financial Disclosure	
		Company	**Relationship**
Bowen, Anna	*Centers for Disease Control and Prevention*	• Procter and Gamble	• Research Support
Pham, Paul	*University of Maryland & Westview Urgent Care Medi Center*	None	• N/A
Sears, Cynthia*	*Johns Hopkins University*	• Clinical Infectious Diseases	• Other
		• Merieux Institute	• Research Support
		• NIH	• Research Support
		• Up-To-Date	• Other
Wanke, Christine	*Tufts University Medical School*	• GlaxoSmithKline	• Research Support
		• Optimer Pharmaceutical	• DSMB
		• Pfizer	• Clinical Trial Even Adjucation

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from April 1, 2014, through April 1, 2016.

Bartonellosis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Basgoz, Nesli	*Harvard Medical School*	• Forest Labs	• Other
Chomel, Bruno	*University of California Davis*	None	N/A
Kirby, James	*Harvard Medical School*	None	N/A
Koehler, Jane*	*University of California San Francisco*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Syphilis (Last Reviewed: February 1, 2016; Last Updated: February 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Bolan, Gail	*Centers for Disease Control and Prevention*	None	N/A
Ghanem, Khalil	*Johns Hopkins University*	None	N/A
Hollier, Lisa	*Baylor College of Medicine*	None	N/A
Hook, Edward W.	*University of Alabama at Birmingham*	• Becton-Dickinson	• Honoraria, Research Support
		• Gen Probe	• Research Support
		• GlaxoSmithKline	• Research Support
		• Merck	• Honoraria
		• Siemens	• Research Support
Sena, Arlene	*University of North Carolina*	None	N/A
Stoner, Brad	*Washington University School of Medicine*	None	N/A
Workowski, Kim*	*Emory University*	• Bristol-Myers Squibb	• Research Support
		• CDC	• Consultant
		• Gilead	• Consultant
		• Vertex	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from February 1, 2014, through February 1, 2016.

Mucocutaneous Candidiasis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Lionakis, Michail*	*National Institutes of Health*	None	N/A
Ostrosky-Zeichner, Luis	*University of Texas Houston*	• Astellas	• Advisory Board, Consultant, Research Support
		• Cape Cod Assoc.	• Research Support
		• Merck	• Advisory Board, Consultant, Research Support, Speaker's Bureau
		• Pfizer	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• T2 Biosystems	• Research Support
Revankar, Sanjay	*Wayne State University School of Medicine*	• Astellas	• Research Support
		• Merck	• Research Support
		• Optimer	• Consultant
		• T2 Biosystems	• Research Support
Sobel, Jack	*Wayne State University School of Medicine*	• Astellas	• Honoraria, Speaker's Bureau
Vazquez, Jose	*Henry Ford Hospital*	• Astellas	• Honoraria, Research Support, Speaker's Bureau
		• Forest	• Advisory Board, Honoraria, Speaker's Bureau
		• Merck	• Honoraria, Research Support, Speaker's Bureau
		• Pfizer	• Honoraria, Research Support, Speaker's Bureau
		• Strativa	• Honoraria, Speaker's Bureau

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Invasive Mycoses (Last Reviewed: November 10, 2016; Last Updated: November 10, 2016)

Member		Financial Disclosure	
		Company	Relationship
Ampel, Neil*	*University of Arizona*	• Nielsen BioSciences	• Research Support
Blair, Janis	*Mayo Clinic Arizona*	None	N/A
Hage, Chadi	*Indiana University*	None	N/A
Hamill, Richard	*Baylor College of Medicine*	None	N/A
Kauffman, Carol	*University of Michigan and VA Ann* Arbor Healthcare System	None	N/A
Pappas, Peter	*University of Alabama at Birmingham*	• Astellas	• Advisory Board, Consulting, Honoraria, Research Support
		• Merck	• Advisory Board, Research Support, Speaker's Bureau
		• Pfizer	• Advisory Board, Research Support
		• T-2 Diagnostics	• Advisory Board
Perfect, John	*Duke University*	• Amplyx	• Consultant, Research Support
		• Astellas	• Advisory Board, Consultant, Honoraria, Research Support
		• Cidara	• Consultant
		• F2G	• Consultant
		• Merck	• Advisory Board, Consultant, Honoraria, Research Support
		• Minnetronix	• Consultant, Research Support
		• Pfizer	• Consultant, Research Support
		• Scynexis	• Consultant
		• TEVA	• Honoraria
		• *Viamet*	• Consultant
		• Vical	• Consultant

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from November 1, 2014, through November 1, 2016.

Herpes (Last Reviewed: February 1, 2016; Last Updated: February 1, 2016) (page 1 of 2)

Member		Financial Disclosure	
		Company	Relationship
Casper, Corey	*University of Washington School of Medicine*	• Centocor	• Research Support
		• GlaxoSmithKline	• Scientific Advisory Board
		• Janssen Pharmaceuticals	• Consultant, Research Support
		• Johnson & Johnson	• Research Support
		• Sanofi Pasteur	• Research Support
		• Temptime	• Scientific Advisory Board
Durand, Christine	*Johns Hopkins*	• Gilead	• Advisory Board, Research Support
Gnann, John	*Medical University of South Carolina*	• BioCryst	• DSMB Member
		• GlaxoSmithKline	• DSMB Member
		• Merck	• DSMB Member, Consultant
Jabs, Douglas	*Icahn School of Medicine at Mount Sinai*	• None	• N/A
Jacobson, Mark	*University of California San Francisco*	• None	• N/A
Johnston, Christine*	*University of Washington*	• Agenus	• Research Support
		• Aicuris	• Research Support
		• Genocea	• Research Support
		• Gilead	• Research Support
		• Vical	• Research Support
Kimberlin, David	*University of Alabama at Birmingham*	• Alios	• Research Support
		• GlaxoSmithKline	• Research Support
Parsons, Christopher	*Louisiana State University School of Medicine in New Orleans*	None	• N/A
Phipps, Warren	*University of Washington School of Medicine*	None	• N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from February 1, 2014, through February 1, 2016.

Herpes (Last Reviewed: February 1, 2016; Last Updated: February 1, 2016) (page 2 of 2)

Member		Financial Disclosure	
		Company	**Relationship**
Wald, Anna	*University of Washington School of Medicine*	• Agenus	• Research Support
		• AiCuris	• Consultant
		• Amgen	• Consultant
		• Eisai	• Consultant
		• Genocea	• Research Support
		• Gilead	• Research Support
		• Merck	• DSMB Member
		• Up To Date	• Other
		• Vical	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from February 1, 2014, through February 1, 2016.

Human Papillomavirus Disease (Last Reviewed: March 1, 2016; Last Updated: March 1, 2016)

Member		Financial Disclosure	
		Company	**Relationship**
Brown, Darron	*Indiana University School of Medicine*	• Merck	• Advisory Board, Honoraria, Patent, Speaker's Bureau
		• PDS, Inc.	• Advisory Board
Cu-Uvin, Susan*	*Brown University*	• CONRAD	• Advisory Board
Dunne, Eileen	*Centers for Disease Control and Prevention*	None	N/A
Einstein, Mark	*Rutgers New Jersey Medical School*	• Baxalta	• Research Support
		• Becton-Dickinson	• Research Support
		• Eli Lilly	• Research Support
		• Inovio	• Advisory Board, Research Support, Travel Support
		• Natera	• Consultant
		• Papivax	• Consultant
		• PDS, Inc.	• Consultant, Research Support, Travel Support
		• Photocure	• Consultant, Research Support, Travel Support
		• Roche Molecular Diagnostics	• Advisory Board, Travel Support
Massad, L. Stewart	*Washington University School of Medicine*	None	N/A
Moscicki, Anna Barbara	*University of California, Los Angeles*	• Merck	• Advisory Board, Honoraria
Palefsky, Joel	*University of California, San Francisco*	• Aura Biosciences	• Advisory Board, Travel Support
		• Hologic	• Research Support
		• Merck	• Advisory Board, Consultant, Research Support, Travel Support
		• Pharmajet	• Advisory Board
		• Qiagen	• Consultant
Stier, Elizabeth	*Boston University Medical Center*	None	N/A
Strickler, Howard	*Albert Einstein College of Medicine*	• BD Sciences, Arbor Vita, MTM/Roche, Norchip AS	• These companies providing free testing in a study of molecular methods for cervical cancer screening in HIV+ women.

Human Papillomavirus Disease (Last Reviewed: March 1, 2016; Last Updated: March 1, 2016)

Member		Financial Disclosure	
		Company	**Relationship**
Wilkin, Timothy	*Weill Cornell Medical College*	• Gilead	• Research Support
		• Bristol Myers Squibb	• Research Support
		• GlaxoSmithKline/ViiV	• Research Support
		•Johnson & Johnson	• Spouse is employee and owns stock.

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from March 1, 2104, through March 1, 2016.

Hepatitis B Virus Infection (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Bhattacharya, Debika	*University of California, Los Angeles*	• International Antiviral Society – USA	• Honoraria
		• Vertex	• Research Support
Jain, Mamta	*University of Texas Southwestern Medical Center*	• AbbVie	• Advisory Board, Research Support
		• Actelion	• Research Support
		• Boehringer Ingelheim	• Advisory Board, Research Support
		• Gilead Sciences	• Advisory Board, Research Support, Speaker's Bureau
		• GlaskoSmithKline	• Research Support
		• Theratechnologies	• Research Support
		• Viiv	• Research Support
Nunez, Marina	*Wake Forest University Health Sciences*	• Bristol Myers Squibb	• Consultant
		• Gilead	• Advisory Board
Peters, Marion*	*University of California, San Francisco*	• Biotron	• Advisory Board
		• Genentech	• Other
		• GReD	• Spouse has relationship
		• International Antiviral Society (IAS-USA)	• Advisory Board
		• Johnson and Johnson	• Honoraria
Thio, Chloe	*Johns Hopkins University*	None	• N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Hepatitis C Virus Infection (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Bansal, Nina	*Mount Sinai Hospital*	None	N/A
Kim, Arthur	*Harvard Medical School*	• Abbvie Pharmaceuticals	• Advisory Board, Consultant, Research Support
		• Bristol-Myers Squibb	• Advisory Board, Consultant
		• Gilead	• Consultant, Research Support
Kim, Nina	*University of Washington*	None	N/A
Naggie, Susanna	*Duke University*	• Abbvie	• Advisory Board, Research Support
		• Achillion	• Consultant, Research Support
		• BMS	• Advisory Board, Research Support
		• Gilead Sciences	• Advisory Board, Research Support
		• Janssen	• Research Support
		• Merck	• Advisory Board, Research Support
		• Vertex Pharmaceuticals	• Research Support
Sulkowski, Mark*	*Johns Hopkins University*	• AbbVie	• Advisory Board, Research Support
		• Bristol-Myers Squibb	• Advisory Board, Research Support
		• Gilead	• Advisory Board, Research Support
		• Janssen	• Advisory Board, Research Support
		• Merck	• Advisory Board, Research Support
Wyles, David	*University of California, San Diego*	• AbbVie	• Consultant, Research Support
		• Bristol-Myers Squibb	• Consultant, Research Support
		• Gilead	• Consultant, Research Support
		• Janssen Pharmaceuticals	• Advisory Board
		• Merck	• Consultant, Research Support
		• Tacere	• Research Support
		• Vertex	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the reviewed date. The period of reporting was from September 1, 2012, through September 1, 2014.

Progressive Multifocal Leukoencephalopathy (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014) (page 1 of 2)

Member		Financial Disclosure	
		Company	Relationship
Cinque, Paola	*San Raffaele Scientific Institute, Milan, Italy*	• Abbott	• Advisory Board, Speaker's Bureau
		• AbbVie	• Advisory Board, Speaker's Bureau
		• Biogen	• Advisory Board, Consultant, Research Support
		• Boehringer Ingelheim	• Advisory Board, Speaker's Bureau
		• Bristol-Myers Squibb	• Speaker's Bureau
		• Gilead	• Speaker's Bureau
		• Janssen-Cilag	• Advisory Board, Speaker's Bureau
		• Johnson & Johnson	• Consultant
		• Merck	• Speaker's Bureau
		• Millenium Pharmaceuticals	• Consultant
		• Pfizer	• Consultant, DSMB Member
		• ViiV Healthcare	• Advisory Board
Clifford, David*	*Washington University School of Medicine*	• Amgen	• Consultant
		• Biogen	• Consultant, Honoraria
		• Bristol-Myers Squibb	• Advisory Board, Consultant
		• Drinker Biddle, Reath LLC	• Advisory Board
		• Genentech	• Advisory Board, DSMB Member
		• Genzyme	• DSMB Member
		• GlaxoSmithKline	• Honoraria
		• Merck Serono	• DSMB Member
		• Millennium	• Consultant, DSMB Member, Honoraria
		• Novartis	• Consultant, Research Support
		• Pfizer	• Consultant, DSMB Member
Marra, Christina	*University of Washington School of Medicine*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014) (page 2 of 2)

Member		Financial Disclosure	
		Company	**Relationship**
Miro, Jose M.	*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain*	• Abbvie	• Consultant, Honoraria, Speaker's Bureau
		• Astellas	• Consultant
		• Bristol-Myers Squibb	• Consultant, Honoraria, Research Support, Speaker's Bureau
		• Cubist	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Fundacion Maximo Soriano Jimenez, Barcelona, Spain	• Research Support
		• Gilead	• Consultant, Honoraria, Speaker's Bureau
		• GlaxoSmithKline	• Honoraria, Speaker's Bureau
		• Instituto de Salud Carlos III, Spanish Ministry of Health, Madrid, Spain	• Research Support
		• Janssen-Cilag	• Speaker's Bureau
		• Merck	• Consultant, Speaker's Bureau
		• NIH	• Research Support
		• Novartis	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Pfizer	• Consultant, Speaker's Bureau
		• ViiV Healthcare	• Honoraria, Research Support, Speaker's Bureau
Nath, Avi	*National Institutes of Health*	None	N/A
Weber, Thomas	*Marienkrankenhaus Hamburg*	• Bayer	• Honoraria, Travel Support
		• Biogen Idec	• Advisory Board, Consultant, Honoraria, Research Support
		• Genzyme	• Honoraria
		• Merck	• Honoraria, Travel Support
		• Novartis	• Honoraria

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Geographic (Last Reviewed: August 1, 2014; Last Updated: August 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Boggild, Andrea	*University of Toronto Department of Medicine*	None	N/A
Dhanireddy, Shireesha*	*University of Washington School of Medicine*	None	N/A
Herwaldt, Barbara	*Centers for Disease Control and Prevention*	None	N/A
Kantipong, Pacharee	*Chiangrai Regional Hospital, Thailand*	None	N/A
Lynch, John	*University of Washington School of Medicine*	None	N/A
Montgomery, Susan	*Centers for Disease Control and Prevention*	None	N/A
Supparatpinyo, Khuanchai	*Chiang Mai University, Thailand*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from August 1, 2012, through August 1, 2014.

Pharmacology (Last Reviewed: November 1, 2016; Last Updated: November 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Dooley, Kelly	*Johns Hopkins University School of Medicine*	• Viiv Healthcare	• Research Support
George, Jomy	*National Institutes of Health*	None	N/A
Kuriakose, Safia	*National Institutes of Health*	None	N/A
Pau, Alice*	*National Institutes of Health*	None	N/A
Peloquin, Charles	*University of Florida*	• Astra Zeneca	• Research Support
		• Jacobus Pharmaceuticals	• Research Support
		• Otsuka	• Advisory Board
Pham, Paul	*Westview Urgent Care*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from November 1, 2014, through November 1, 2016.

Pregnancy (Last Reviewed: March 1, 2016; Last Updated: March 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Anderson, Jean	*Johns Hopkins University*	• Gilead	• Scientific Advisory Board
Cohan, Deborah	*University of California San Francisco*	None	N/A
Hughes, Brenna	*Women & Infants Hospital of Rhode Island*	None	N/A
Watts, Heather*	*Office of the Global AIDS Coordinator*	None	N/A
Wright, Rodney	*Albert Einstein College of Medicine*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from March 1, 2014, through March 1, 2016.

Immunizations (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Kim, David*	*Centers for Disease Control and Prevention*	None	N/A
Peters, Philip	*Centers for Disease Control and Prevention*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Appendix D. Contributors

As part of the revision process, a Clinical-Community Panel was convened to review these guidelines and advise the author panel as to their usefulness for practicing clinicians with regard to content and format. The members of the Clinical Community Panel are as follows:

- Roberto Arduino; Thomas Street Health Center—Houston, Texas
- Mark Baker; MedStar Washington Hospital Center—Washington, DC
- Lisa Fitzpatrick; Howard University—Washington, DC
- C. Bradley Hare; San Francisco General Hospital and University of California, San Francisco—San Francisco, California
- Robert Harrington; University of Washington—Seattle, Washington
- E. Turner Overton; Washington University—St. Louis, Missouri
- David Rimland; Emory University—Atlanta, Georgia
- Martin Rodriguez, University of Alabama at Birmingham—Birmingham, Alabama
- Peter Shalit; Swedish Hospital Medical Center HIV Program—Seattle, Washington
- Tracy Swan; Treatment Action Group—New York, New York
- Zelalem Temesgen; Mayo Clinic—Rochester, Minnesota
- Mary Vogler; Weill Cornell—New York, New York
- Dan Wlodarczyk; University of California, San Francisco—San Francisco, California

The panel would like to acknowledge Judith Welsh, Clinical Informationist at the National Institutes of Health Library, for performing comprehensive literature searches to identify the evidence used to support recommendations in these guidelines.