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

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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).

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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:

November 10, 2016

1. **Coccidioidomycosis:** The guideline was rewritten to update recommendations for various types of coccidioidomycosis. It emphasizes that in HIV-infected persons with CD4 counts >250/µL, coccidioidomycosis can be managed in the same manner as in those without HIV infection. The triazole antifungals fluconazole and itraconazole remain the mainstays of treatment. Antiretroviral therapy in patients with coccidioidomycosis should not be delayed because of concern for immune response inflammatory syndrome.

August 17, 2016

1. **Cryptococcosis:** In this revision, new data is cited that found that there was no improvement with the addition of a six-week tapering course of dexamethasone to antifungal therapy among African and Asian patients with cryptococcal meningitis. This supports the current guideline recommendations to not use corticosteroids in cryptococcal meningitis in the absence of the immune response inflammatory syndrome.

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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]

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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).

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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.

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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

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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 **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes **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,

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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.

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

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.

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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)**.

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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.

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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;

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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

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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)**.

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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)**.

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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)**

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

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

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

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

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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

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(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.

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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

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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

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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.*

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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)

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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 Regimen:

- 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

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

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.

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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

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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

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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)**.

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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

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

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

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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

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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

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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

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Mycobacterium tuberculosis Infection and Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

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

In individuals with LTBI, the risk of reactivation with TB disease increases very soon after HIV infection.[1] The estimated annual risk of reactivation with TB disease among those with untreated HIV infection and LTBI is 3% to 16% and approximates the lifetime risk for HIV-uninfected individuals with LTBI (~5%).[2] TB disease can occur at any CD4 T lymphocyte (CD4 cell) count, although the risk increases with progressive immunodeficiency.[3]

Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, an effect that has been documented in settings with low[4] and high case rates.[5,6] Even with the beneficial effects of ART, HIV-infected patients remain at higher risk of TB disease than the general population.[7]

Rates of TB in the United States are declining, with 3.6 new cases per 100,000 population reported in 2010[8] (a total of 11,182 cases). The prevalence of LTBI in the general population of the United States is 4%.[9] The incidence of HIV-related TB has declined more rapidly than the rate of active TB in the general population,[10] which is probably related to the widespread use of ART. In recent years there have been fewer than 1000 new cases of HIV/TB co-infection identified per year in the United States.[8,11,12]

As with TB in the general U.S. population, HIV-related TB disease is increasingly seen in people born outside of the United States.[10] Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.[10,13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. In the era of potent ART, TB disease remained the second most common initial opportunistic illness in New York City.[14] Unlike most opportunistic infections (OIs), TB is transmissible, particularly to others who are HIV-infected. Therefore, clinicians caring for patients 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 cotreatment of HIV and TB.

Preventing Exposure

The most common predisposing factor for TB is birth or residence outside of the United States. 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 testing for LTBI upon return **(AIII)**. Although some health care and correctional settings in the United States present risks of TB exposure, HIV-infected individuals need to take no precautions beyond those recommended for anyone in those environments **(AIII)**.

Preventing Disease–Diagnosis and Treatment of Latent TB Infection

The estimated annual risk of active TB among HIV-infected patients with LTBI is 3 to 12 times higher than for the general population.[15,16] Furthermore, development of HIV-related TB increases viral load[17] and the risk of HIV disease progression[17] and death[18] compared with CD4-matched, HIV seropositive controls.

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Among HIV-infected individuals, treatment of LTBI decreases the risk of TB disease by 62% and the risk of death by 26%.[19] Therefore, prevention of TB disease by screening for and appropriately treating LTBI is a key component of HIV care.

Diagnosis of Latent Tuberculosis Infection

Testing for LTBI at the time of HIV diagnosis should be routine, regardless of an individual's epidemiological risk of TB exposure. Individuals with negative diagnostic tests for LTBI who have advanced HIV infection (CD4 cell count <200 cells/mm^3) and no indications for initiating empiric LTBI treatment should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3.[20,21] Annual testing for LTBI is recommended only for HIV-infected patients who are at high risk of repeated or ongoing exposure to those with active TB.

Traditionally, LTBI has been defined by the presence of a positive tuberculin skin test (TST) (≥5 mm of induration at 48–72 hours) in individuals with no clinical or radiographic evidence of TB disease. Although experience with the TST in HIV-infected individuals is extensive, it has several disadvantages: the requirement for two visits to place and read the test, decreased specificity in those who received Bacillus Calmette-Guerin (BCG) vaccination, and decreased sensitivity in those with advanced immunodeficiency.[22] Limitations of the TST have led to interest in interferon-gamma release assays (IGRAs) for detection of LTBI.

Current evidence suggests that IGRAs have higher specificity (92%–97%) than TST (56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*,[23] and less cross reactivity because of BCG vaccination or other non-tuberculous mycobacteria exposure.[24,25] Three IGRAs are Food and Drug Administration (FDA) approved and available in the United States. Progressive immunodeficiency is associated with decreased sensitivity of IGRAs, although immunodeficiency may have less impact on the sensitivity of IGRAs than on the sensitivity of TST.[26]

In HIV-infected patients, the correlation between TST and IGRAs is poor to moderate.[27,28] In prospective studies, positive results with either TST or IGRA were associated with an increased risk of developing TB disease;[29,30] 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.[31,32] For all of its limitations, TST response remains strongly predictive of response to isoniazid preventive therapy among those with HIV infection.[19] 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.[33-35] A higher proportion of patients may complete screening for TB if testing is done with IGRAs.

No definitive comparisons have been done of TST and IGRAs for screening HIV-infected individuals in low-burden settings such as the United States. Both TST and the FDA-approved IGRAs are appropriate for TB screening in HIV-infected individuals.[36] Some experts have suggested using both TST and IGRA to screen for LTBI, but the predictive value of this approach is unclear, and it would be more expensive and more difficult to implement. Routine use of both TST and IGRAs to screen for LTBI **is not recommended** in the United States.[36]

Patients with TB disease often demonstrate immune reactivity against *M. tuberculosis* in TST and IGRA testing. Therefore, any positive result with TST or IGRA should trigger expeditious evaluation for the possibility of active TB. Most, but not all, HIV-infected individuals with TB disease have symptoms; the absence of any symptoms has a 97% negative predictive value for culture-positive TB.[37] The addition of a chest radiograph improves the sensitivity of symptom screening algorithms. Sputum culture is the gold standard for diagnosing pulmonary TB disease but is not cost effective for screening HIV-infected patients who are asymptomatic, particularly in the United States, where TB prevalence is very low. Therefore, screening for symptoms (asking for cough of *any* duration) coupled with chest radiography is recommended to exclude TB disease in a patient with a positive TST or IGRA.

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When to Start Primary Prophylaxis (i.e., Treating Latent Tuberculosis Infection)

HIV-infected individuals who test positive for LTBI but have no evidence of TB disease should receive LTBI treatment **(AI)**. HIV-infected close contacts of anyone who has infectious TB also should receive prophylaxis, regardless of results of screening tests for LTBI **(AII)**. Notably, for HIV-infected individuals who are anergic and have not had recent contact with anyone with infectious TB, treatment of LTBI is not associated with clinical benefit and **is not recommended** **(AI)**.[38-41]

Preferred and Alternative Drugs for Treatment of Latent Tuberculosis Infection

Isoniazid administered for 9 months remains the preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AII)**. Isoniazid can potentiate the risk of peripheral neuropathy when used with some antiretroviral (ARV) drugs, most notably the dideoxynucleosides (didanosine, stavudine), which are seldom used in clinical practice in the United States. Isoniazid, when used with efavirenz- or nevirapine-based regimens, does not significantly increase risk of hepatitis—the most important adverse effect.[42,43] Isoniazid should be supplemented with pyridoxine at a dose of 25 mg/day to prevent peripheral neuropathy **(AIII)**. A significant disadvantage of the 9-month regimen is that most patients in the United States and Canada do not complete all 9 months of therapy.[44-46] Shorter regimens are more likely to be completed.[44-46] Recent data from an open-label, randomized non-inferiority trial comparing a 3-month regimen of isoniazid plus rifapentine, given by directly observed therapy (DOT) once weekly, with a 9-month regimen of self-administered once daily isoniazid demonstrated that, after 33 months of follow-up, the 3-month isoniazid-rifapentine regimen was as effective as the 9-month isoniazid regimen.[47] The shorter course regimen had the advantage of a higher completion rate. These results led to a recent Centers for Disease Control and Prevention (CDC) recommendation that 3-months of once weekly isoniazid-rifapentine given by DOT can be used as an equal alternative to the standard 9-month regimen.[48] However, the 3-month regimen **is not recommended** for HIV-infected patients receiving ART because of potentially significant drug interactions between rifapentine and some ARV drugs **(AIII)**.[48] Other alternative therapies for chemoprophylaxis are shown in Table 1; the regimen of 2 months rifampin plus pyrazinamide **is not recommended** because of the risk of severe and sometimes fatal hepatotoxicity **(AII)**. Rifampin- or rifabutin-containing regimens may require dose adjustments of ARV or rifabutin (Table 5).

LTBI treatment and ART act independently to decrease the risk of TB disease.[49-51] Therefore, use of both interventions is recommended for those who have LTBI and an indication for ART **(AII)**.

Monitoring of Response to Treatment of Latent Tuberculosis Infection

Patients receiving daily LTBI treatment through self-administration should be seen by the prescribing clinician on a monthly basis to assess adherence and evaluate for possible drug toxicity; generally, not more than 1 month's supply of drugs should be prescribed. Individuals taking a twice-weekly regimen should receive LTBI treatment by direct observation. Risk of hepatitis from isoniazid prophylaxis may not be higher in HIV-infected individuals than those who are uninfected, but baseline measurements of serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin are recommended, and if results are abnormal, testing should be repeated.[52] Individuals with concomitant chronic viral hepatitis may be at increased risk of isoniazid-related hepatotoxicity, and they should be treated for LTBI and closely monitored. With isoniazid, liver enzymes typically increase in the first 3 months but then (through the process of hepatic adaptation) return to normal despite continued therapy. LTBI treatment should be stopped in asymptomatic patients who have a more-than-fivefold increase in AST levels above the upper limit of normal (ULN), symptomatic patients who have a more-than-threefold increase above ULN in AST levels, and patients regardless of symptoms with baseline abnormal transaminases who have a more-than-twofold increase above their baseline AST levels. Patients should be reminded at each visit about potential adverse effects (i.e., unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 days or more, abdominal tenderness, easy bruising or bleeding, and arthralgia) and told to immediately stop isoniazid and return to the clinic for an assessment.

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The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk of additional hepatic injury against the benefit of preventing progression to TB disease[52] and in consultation with an expert in treating LTBI.

Clinical Manifestations of Tuberculosis Disease

Common clinical symptoms of TB disease include productive cough, fever, sweats, weight loss, and fatigue. Culture-positive TB disease can be sub-clinical or oligo-symptomatic.[37] After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection.

In HIV-infected individuals, the presentation of active TB disease is influenced by the degree of immunodeficiency.[53,54] In HIV-infected patients without pronounced immunodeficiency, (that is, CD4 cell counts >350 cells/mm^3), HIV-related TB clinically resembles the disease seen in HIV-uninfected patients. Most patients have disease limited to the lungs, and common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation.[55] Extrapulmonary disease is more common in HIV-infected individuals than in those who are uninfected, regardless of CD4 cell counts, although clinical manifestations are not substantially different from those described in HIV-uninfected individuals. TB must be considered in disease processes involving any site in the body,[56] but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.[57,58]

In patients with advanced HIV disease, the chest radiographic findings of pulmonary TB are markedly different than those in patients with less severe immunosuppression. Lower lobe, middle lobe, interstitial, and miliary infiltrates are common and cavitation is less common.[53,55,59] Intrathoracic lymphadenopathy is common, with mediastinal involvement seen more often than hilar adenopathy. Even with normal chest radiographs, patients with HIV infection and pulmonary TB may test positive on acid-fast bacilli (AFB) sputum smears and cultures, particularly if they have cervical node involvement.

The greater the degree of immunodeficiency, the higher the likelihood of extrapulmonary TB, such as lymphadenitis; pleuritis; pericarditis; and meningitis, all with or without pulmonary involvement, and it is found in most TB patients with CD4 cell counts <200 cells/mm^3.[54] In these individuals, TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.[60]

Histopathologic findings also are affected by the degree of immunodeficiency. Patients with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or may be completely absent.[54]

Diagnosis of Tuberculosis Disease

Initial diagnostic testing is directed at the anatomic site of symptoms or signs, such as the lungs, lymph nodes, and cerebrospinal fluid (CSF). Even in the absence of pulmonary symptoms or signs, the initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph; pulmonary involvement is common whatever the CD4 cell count.[37,61] However, chest radiography is an imperfect screen for sputum culture-positive TB, particularly in patients with advanced immunodeficiency. Therefore, sputum smear and culture should be considered in symptomatic patients with normal chest radiographs who are being evaluated for possible TB disease.

Sputum smear-negative TB is common in HIV-infected patients, particularly those with advanced immunodeficiency and noncavitary disease.[62] 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. 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.[63]

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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.[64] Pleural fluid, pericardial fluid, ascites, and CSF should be sampled if there is clinical evidence of involvement. The yield of mycobacterial urine and blood cultures depends upon the clinical setting; in patients with advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high[54,56] and may allow definitive diagnosis and a source for an isolate for drug-susceptibility testing.

Nucleic-acid amplification (NAA) tests provide rapid diagnosis of TB, in contrast to the prolonged time needed for detection of mycobacterial growth, and can be considered for patients with advanced immunodeficiency who are at risk of rapid clinical progression of TB (some assays also provide rapid detection of drug resistance as discussed below). NAA tests have at least two uses in patients with suspected HIV-related TB. First, they are highly predictive of TB in specimens that are AFB smear-positive. Non-tuberculous mycobacterial infections are relatively common in patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation in patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, producing positive results for 50% to 80% of smear-negative, culture-positive specimens.[65,66] Therefore, the use of a NAA test is recommended on at least one specimen from all patients being evaluated for suspected pulmonary TB.[67] The NAA tests currently available are licensed only for evaluation of sputum samples; much less experience exists with samples from extrapulmonary sites.

Immunological screening for TB with TST and IGRA may be helpful in unusual circumstances that make it difficult to obtain definitive culture evidence for active TB; evidence of prior infection increases the likelihood that a clinical illness may be TB. A negative test, however, should never be interpreted as ruling out TB disease.

Drug-susceptibility testing should be performed on the initial isolates from all patients suspected of having TB because 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.[68] 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.[69] Thus, early identification of drug resistance, with appropriate adjustment of therapy based on results, is critical to successfully treating TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.

Drug-susceptibility testing to first-line TB drugs (i.e., isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed on all patients with TB disease, regardless of the source of the specimen. These tests 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. Drug susceptibility testing for second-line TB medications (e.g., fluoroquinolones, aminoglycosides, capreomycin, ethionamide) should be performed only in reference laboratories that have substantial experience with these techniques and should be limited to specimens with resistance to first-line TB medications.

Conventional drug-susceptibility testing is widely used and has been well validated for first-line drugs. The disadvantage of this technique, however, is the combined turnaround time for culture and drug-susceptibility testing, which can be as long as 6 weeks[70] because of the slow growth of *M. tuberculosis* in culture. 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.[69]

Genotypic testing, which identifies drug-resistance mutations, allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications,[71] and commercial tests have been developed and validated to identify genotypic resistance for rifampin[65,72] and isoniazid.[72] Development is under way of commercial tests to identify genotypic resistance to other TB

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medications.[73] Genotypic assays can provide a result in 24 hours and can be performed directly on sputum specimens.

Clinicians who suspect that an HIV-infected patient has drug-resistant TB should make every effort to expedite diagnosis. In the United States, the CDC Division of TB Elimination has a Molecular Detection of Drug Resistance service to make rapid molecular testing for first-and second-line TB medications available for patients who have or are suspected to have TB and do not have local access to such testing (http://www.cdc.gov/tb/topic/laboratory/default.htm).

Drug resistance should be considered in any patient with:

- known exposure to an individual with drug-resistant TB
- residence in a setting with high rates of primary drug-resistant TB, such as a country or area with high rates of drug-resistant TB in newly diagnosed patients[74]
- 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.

Treating Disease

In some settings in the United States, non-tuberculous mycobacterial infections are more common than TB among HIV-infected patients. However, because TB is highly virulent and represents a greater risk of transmission to others, treatment for it is more urgent than for non-tuberculous mycobacterial infections. Furthermore, first-line TB drugs are highly active against *Mycobacterium kansasii*, a relatively common non-tuberculous mycobacterial infection that presents clinically and radiographically like TB.[75] Finally, with appropriate access to broth culture and molecular diagnostics (NAA and genotypic tests for resistance), the time between finding a smear-positive specimen and identifying the species should be short.

TB in individuals with advanced immunodeficiency can be rapidly progressive and fatal if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens. 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 in HIV-infected individuals is the same as for those who are HIV uninfected and should include an initial four-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol **(AI)**. An expanded initial regimen—including at least moxifloxacin or levofloxacin and an aminoglycoside or capreomycin—should be used if there is a significant concern about resistance to rifampin, with or without resistance to other drugs **(BIII)**. A TB expert should be consulted if drug resistance is suspected. 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 (i.e., enhanced DOT).

Drug-susceptible TB is treated with a 2-month intensive phase of the 4 drugs previously listed. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Pyrazinamide may be discontinued after 2 months. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy.

Intermittent dosing (administration less often than daily) of anti-TB treatment facilitates DOT. However, 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.[76-78] Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase **(AII)**.

Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase of therapy **(AII)**. Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were

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associated with increased risk of treatment failure or relapse with acquired rifamycin resistance.[79,80] 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; in observational studies and a meta-analysis, thrice-weekly therapy during the continuation phase was not associated with an increased risk of adverse TB outcomes (i.e., treatment failure, recurrence, or acquired drug resistance).[81]

The optimal duration of TB treatment for patients with HIV infection and drug-susceptible TB disease is unknown. In general, the outcomes have been good with 6-month regimens (2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV co-infection. 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.[82] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy compared with those assigned to 9-[76] or 12-month regimens.[83] However, the applicability of these two trials is uncertain in low-burden settings in which ART is used, such as the United States.

Pending the outcome of further studies, 6 months of therapy for most patients with HIV-related, drug-susceptible TB disease is recommended **(BII)**. Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture **(BII)**. Extension of therapy to 9 to 12 months is also recommended for patients with CNS involvement **(BII)**. Treatment for 6 to 9 months is recommended for patients with bone and joint TB **(BII)**. The duration of therapy should be based on number of doses received, not on calendar time **(BIII)** because there may be substantial differences between dose number and calendar time if doses were missed due to poor adherence or for management of problems with tolerability or toxicity.

Adjunctive corticosteroid therapy increases survival for patients with HIV-related TB involving the CNS[84] and pericardium[85] **(AI)**. No trials to date have compared 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 g/day and taper 10 mg per week; total duration of 6 weeks).

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed; sequential treatment of TB followed by HIV treatment **is not recommended**.[86] 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 ARV drugs, overlapping side effect profiles of antituberculosis and ARV drugs, and the frequency of immune reconstitution inflammatory syndrome (IRIS). Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival,[86] particularly in patients with CD4 counts <50 cells/mm^3; decreases the risk of additional opportunistic illnesses including TB;[87] can achieve high rates of viral suppression;[88] and may improve TB treatment outcomes.[89]

Starting ART early in the course of TB treatment can complicate clinical management because of increased pill burden, drug toxicities, drug interactions, and IRIS events. However, recently completed randomized clinical trials demonstrate that ART can be safely given during TB treatment without jeopardizing HIV treatment responses and that ART reduces mortality and HIV-related illnesses.[86-88]

The SAPIT trial randomized 642 South African adults with CD4 cell counts <500/mm^3 and AFB smear-positive TB to start ART according to one of three strategies; at TB treatment initiation; after the intensive phase of TB therapy but before TB treatment completion; or after TB treatment completion.[86] The study was stopped early when the mortality of the 2 integrated treatment arms was 56% lower than the sequential treatment arm, demonstrating that ART should be started before completion of TB treatment. Notably, there was a survival benefit across the range of CD4 cell counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500 cells/mm^3. Updated results of the SAPIT trial indicated that the benefit of early ART was greatest for those with CD4 counts of <50 cells/mm^3 and that individuals with

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higher CD4 cell counts who started ART within the first 4 weeks of the continuation phase of TB treatment had a lower incidence of IRIS and adverse events.[90]

The CAMELIA and A5221 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 count of 25 cells/mm^3 (interquartile range [IQR] 10,56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The risk of death was decreased from 27% in the 8-week arm to 18% in the 2-week arm and, among those who survived, viral suppression rates were very high (>95%).[88] The ACTG A5221 study randomized 809 patients from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 count of 77 cells/mm^3 (IQR 33,146) to immediate ART (within 2 weeks) or early ART (8–12 weeks).[87] 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 counts <50 cells/mm^3, 15.5% of patients on the immediate arm versus 26.6% on early ART experienced AIDS or death, ($P = 0.02$). Tuberculous-associated IRIS (TB-IRIS) was more common in the immediate ART arm (11%) compared with the early arm (5%) ($P = 0.002$). Viral suppression rates were similar between the arms.

Other recently completed smaller and non-randomized studies provide further support for early ART initiation. In the PART study, which included only patients with TB and HIV with CD4 cell counts >350 cells/mm^3, even a short 6-month course of ART started at TB diagnosis resulted in lower rates of AIDS or death compared with delaying ART until a CD4 threshold of 250 cells/mm^3.[91] A recent retrospective analysis of HIV-infected adults with XDR TB showed a 62% reduction in mortality in those who received ART.[92]

The optimal strategy in TB meningitis is less clear. A randomized trial conducted in Vietnam compared ART initiated immediately or 2 months after starting TB treatment in 253 patients with HIV-related TB meningitis.[93] This study did not show a survival benefit for early initiation of ART. On the contrary, early ART was associated with significantly more severe adverse events (102) compared with the deferred ART arm (87; $P = 0.04$). The overall mortality rates and severe adverse event rates in this study were extraordinarily high (58% and 89–90%, respectively), in part reflecting the very ill AIDS population, and may not be generalizable to other settings. Nonetheless, caution in early ART initiation is warranted in patients with tuberculous meningitis.

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 of drug interactions and maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed and a new ART regimen constructed, along with intensified adherence counseling to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

In summary, ART is recommended in all HIV-infected persons with TB **(AI)**. For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm^3 and by 8 to 12 weeks for all others **(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 that calls for careful monitoring and consultation with experts. 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.

Drug-drug interactions in the treatment of HIV-related tuberculosis

The rifamycin class of antibiotics is the key to effective, short-course TB treatment. However, the rifamycins currently available (rifampin, rifabutin, and rifapentine) have clinically significant interactions with a number of ARV drugs (Table 5). 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 ARV agents.

The preferred cotreatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz plus two nucleoside(tide) analogues **(AII)**. Efavirenz-based ART is associated with

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excellent TB and HIV treatment outcomes and has low rates of serious toxicity.[94] Data conflict on the magnitude of the change in efavirenz concentrations when co-administered with rifampin. Early studies reported a 26% reduction in efavirenz exposure,[95] 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 on efavirenz exposure.[96,97] Previous recommendations to increase the dose of efavirenz, especially in patients who weigh >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, and emtricitabine, and possibility of increased neuropsychiatric side effects. Given the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[94,98] the 600-mg daily dose of efavirenz is recommended **(BII)**.

Rifampin has a more significant effect on the concentration of nevirapine, but clinical outcomes have been reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an ARV regimen of nevirapine plus two nucleoside analogues.[94,99,100] However, a recent randomized controlled trial showed that a once daily nevirapine regimen used with didanosine and lamivudine was inferior to a once daily efavirenz regimen used with the same NRTIs in HIV-associated TB treated with a rifampin regimen.[101] For patients absolutely unable to take efavirenz due to intolerance or early pregnancy, nevirapine-based ART can be used, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin for at least 2 weeks and plasma HIV RNA levels should be monitored closely.[94]

For patients who have HIV strains resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or are unable to tolerate efavirenz and nevirapine, the preferred co-treatment regimen is rifabutin-based TB therapy with an ARV regimen that includes a ritonavir-boosted protease inhibitor (PI) **(BIII)**. The dramatic effects of rifampin on serum concentrations of lopinavir can be overcome by high-dose ritonavir,[102] but high rates of hepatotoxicity have been reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[103-105] Rifabutin has little effect on ritonavir-boosted lopinavir[106] or atazanavir,[107] and its co-administration results in moderate increases in darunavir[108] and fosamprenavir concentrations.[109]

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.[110] The magnitude of the dose reduction for rifabutin remains somewhat controversial. In studies of healthy volunteers, a 150-mg dose every other day together with a ritonavir-boosted PI achieved serum concentrations of rifabutin comparable to or higher (with much higher concentrations of the desacetyl metabolite) than those achieved with 300 mg rifabutin daily in the absence of a PI.[108,109,111] However, among HIV-infected individuals with TB, there have been case reports of acquired rifamycin resistance with 150-mg thrice-weekly dosing in the presence of a boosted PI-based ARV regimen.[112,113]

Pending additional data, we recommend a dosage of 150 mg of rifabutin daily (at least during the first 2 months of TB treatment) for patients who are on a PI-containing ARV regimen **(BIII)**. Therapeutic drug monitoring for rifabutin can be considered in this situation.[113] Close monitoring of adherence to ART is important because these reduced doses of rifabutin would be inadequate if patients stopped taking the PI.

Clinical experience is minimal for use of rifamycins with raltegravir, CCR5 receptor antagonists, and second-generation NNRTIs. Raltegravir concentrations are decreased when coadministered with rifampin, and a raltegravir dose increase (to 800 mg twice daily [BID]) is recommended but has not been evaluated in clinical trials. Similarly, there is no published experience with rifampin or rifabutin and elvitegravir boosted with cobicistat, although the drug interactions and required dose adjustments are expected to be similar to those with boosted PIs. These ARV drugs should be used only when required for ARV potency and in consultation with an expert in this field. As new antiretroviral drugs are approved, recommendations will be developed about their use in conjunction with antituberculous regimens.

The breadth and magnitude of drug-drug interactions between the rifamycins and many ARV drugs can be daunting. Nevertheless, every effort should be made to include a rifamycin in the TB treatment regimen; the

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drug-drug interactions between rifamycins and ARV 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 recurrence among patients with HIV-related TB.[114,115] Patients with rifamycin-susceptible *M. tuberculosis* isolates should only be treated with a regimen that does not contain a rifamycin if they have had a serious event that is highly likely to be due to the drug.

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

Patients with pulmonary TB should have monthly sputum smears and cultures to document culture conversion on therapy (defined as two consecutive negative cultures). Sputum cultures typically convert to negative in patients with susceptible TB within the first 2 months of first-line TB therapy; sputum culture conversion may take longer in patients with a high burden of disease, such as cavitary TB disease.[116] Patients who have not had sputum culture conversion at or after 4 months of therapy should be evaluated for possible treatment failure and acquired drug resistance.

Adverse events during the treatment of HIV-related TB are common.[52,117-120] Because alternative drugs often have less efficacy and more toxicities than first-line anti-TB drugs and diagnosing a drug reaction and determining the responsible agent can be difficult, the first-line drugs (especially isoniazid, rifampin, or rifabutin) should not be stopped permanently without strong evidence that a specific anti-TB drug was the cause of the reaction. In such situations, consultation with a specialist in treating TB disease in HIV-infected individuals is recommended.

Gastrointestinal (GI) reactions are common with many of the anti-TB medications.[121] If GI symptoms occur, AST and bilirubin should be measured to determine if hepatic toxicity is the cause. Typically, GI symptoms not related to hepatic toxicity should be managed without discontinuing TB medications; initial approaches should include either changing the time of administration or administering drugs with food.

Skin rashes are common with all anti-TB drugs. If rash is minor, affects a limited area, or causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications continued. If the rash is severe, all TB medications should be stopped until the rash is substantially improved, and TB drugs restarted one by one at intervals of 2 to 3 days. Rifampin or rifabutin should be restarted first because their role in treatment is critical. If the rash recurs, the last drug that had been added should be stopped. If a petechial rash thought to be caused by thrombocytopenia occurs, rifampin or rifabutin should be stopped permanently.[122] If a generalized rash associated with either fever or mucous membrane involvement occurs, all drugs should be stopped immediately, patients should be switched to alternative anti-TB agents, and LTBI or TB treatment should be managed in consultation with a specialist.

Fever in HIV-infected patients who have been receiving effective TB therapy for several weeks may represent drug fever, another infection, or IRIS.[123] If superinfection or worsening TB is excluded as a potential cause, all TB drugs should be stopped. Once the fever has resolved, the general guidelines described for restarting/stopping drugs in the presence of a rash should be followed.

An increase in AST occurs in approximately 20% of patients treated with the standard four-drug, anti-TB regimen.[124] Drug-induced liver injury can be caused by isoniazid, rifamycins, pyrazinamide, or a number of ARV drugs. Drug-induced liver injury is defined as an AST elevation to ≥3 times the ULN or baseline (whichever is higher) in the presence of symptoms, or >5 times the ULN in the absence of symptoms.[125] In addition to AST elevation, disproportionate increases in bilirubin and alkaline phosphatase occasionally occur. This latter pattern is more consistent with rifamycin hepatotoxicity than with isoniazid or pyrazinamide hepatotoxicity. In most patients, asymptomatic aminotransferase elevations spontaneously resolve.

In the absence of symptoms, elevations of AST <3 times ULN should not prompt changes of TB therapy, but the frequency of clinical and laboratory monitoring should be increased. If AST levels are ≥5 times the ULN regardless of symptoms, >3 times the ULN with symptoms, or if a significant increase in bilirubin and/or alkaline phosphatase occurs, hepatotoxic drugs should be stopped and patients should be evaluated

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immediately. For any substantial new transaminase or bilirubin elevation, serologic testing for hepatitis A, B, and C should be performed, and patients should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins.

If anti-TB drugs must be stopped for hepatotoxicity, it may be prudent to substitute more than three nonhepatotoxic anti-TB drugs (depending on the stage of TB therapy, the degree of clinical illness, and the severity of immunodeficiency) until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed. The anti-TB medications should be restarted one at a time after the AST level returns to <2 times the ULN or to near baseline for patients with pre-existing abnormalities. Because the rifamycins are a critical part of the TB regimen and are less likely to cause hepatotoxicity than isoniazid or pyrazinamide,[45,124] they should be restarted first. If no increase in AST occurs after 1 week, isoniazid may be restarted. Pyrazinamide can be restarted 1 week after isoniazid if AST does not increase. If symptoms recur or AST increases, the last drug added should be stopped. If rifampin and isoniazid are tolerated and hepatitis was severe, pyrazinamide should be presumed responsible and should be discontinued. In this last circumstance, therapy can be extended to 9 months with rifampin and isoniazid alone, depending on the number of doses of pyrazinamide taken, severity of disease, and bacteriological status.

In patients with recently diagnosed or undiagnosed active TB, TB-IRIS is a common early complication. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[126-128] 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 case definitions for these syndromes have been published.[129]

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB before starting ART. Typically, these patients have had clinical improvement on TB treatment before starting ART. Within the first weeks of ART (though sometimes later) they develop new or recurrent symptoms and new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include hectic fevers, new or worsening lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality from paradoxical TB-IRIS is uncommon,[127,130] 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.[127,131,132] In patients with disseminated TB, hepatic TB-IRIS is common and manifests with tender hepatic enlargement, nausea and vomiting, cholestatic liver function derangement, and occasionally jaundice.[133,134] On liver biopsy, a granulomatous hepatitis is demonstrated. Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common in patients starting ART while on TB treatment (8%–43%). A recent meta-analysis provided a pooled estimate of incidence of IRIS of 15.7%, with a case fatality rate of 3.2%.[130] Onset of paradoxical TB-IRIS symptoms typically occurs 1 to 4 weeks after ART is initiated.[135-140] On average, the syndrome lasts for 2 to 3 months,[131,141] but some patients have symptoms for months and, in rare cases, local manifestations may persist or recur more than a year after onset.[129,141,142]

The most consistently identified risk factors for paradoxical TB-IRIS are low CD4 cell count at start of ART (especially CD4 cell counts <100 cells/mm^3);[133,143] disseminated or extrapulmonary TB;[131,137,139,143] and a short interval between starting TB treatment and ART, particularly within the first 2 months of TB treatment.[131,136,138]

The diagnosis of paradoxical TB-IRIS can 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 features of TB soon after starting ART; demonstration of a response to ART (CD4 rise and/or viral load reduction); and, most important, investigations to exclude alternative causes for deterioration, particularly undetected TB drug resistance.

Most cases of paradoxical TB-IRIS are self-limiting. Many patients require symptomatic therapy (analgesia, antiemetics) and, if symptoms are significant, anti-inflammatory therapy should be considered. One

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randomized, placebo-controlled trial among patients with moderately severe paradoxical 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 of a combined endpoint of days hospitalized plus outpatient therapeutic procedures.[144] Those on prednisone experienced more rapid symptom and radiographic improvement. No mortality benefit was demonstrated, but immediately life-threatening cases, such as those with neurological involvement, were excluded from this study. The above study,[144] observational data,[132] and clinical trials of patients treated with corticosteroids at the time of TB meningitis presentation (in which corticosteroids reduced mortality)[84] suggest that corticosteroids should be used for TB-IRIS involving the CNS. For a minority of patients, 4 weeks of prednisone is insufficient, and they may require more gradual tapering of steroids over a few months **(BIII)**.[144] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms and markers of inflammation, such as fever and tachycardia **(BIII)**. Corticosteroids should be avoided in patients with Kaposi sarcoma[145] and where the diagnosis of paradoxical TB-IRIS is not certain.

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 symptomatic relief. Repeated aspirations may be required because collections and effusions often reaccumulate.[131]

Unmasking TB-IRIS can occur in patients who have unrecognized TB at the time they start ART (because it is sub-clinical, is oligo-symptomatic, or the diagnosis has been missed). These patients present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[129] A common presentation is pulmonary TB presenting with rapid symptom onset and clinical features similar to bacterial pneumonia, with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.[129,146-148] Focal inflammatory manifestations such as abscesses and lymphadenitis also may develop.[149] The treatment is standard TB treatment and corticosteroids if the manifestations are life threatening, although there is no clinical trial evidence to support their use **(BIII)**.

Managing Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, prescription of an incorrect or inadequate regimen, subtherapeutic drug levels due to malabsorption or drug interactions, superinfection 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 they have clinically responded to therapy, even though their cultures have not converted. The initial culture results and drug-resistance tests, treatment regimen, and adherence also should be reviewed. Samples from all available sites 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 superinfection with a drug-resistant strain.

Pending 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)**.

Managing drug-resistant tuberculosis

Clinical trials are needed 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 to these medications develops, alternative combinations of first- and second-line TB medications must be used, but their optimal use has not been tested using rigorous clinical trials.

The standard first-line TB regimen initially was believed to be adequate for isoniazid mono-resistant TB. However, growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid resistance,[150] particularly in patients with HIV co-infection.[76] Substitution of a fluoroquinolone (levofloxacin or moxifloxacin) for isoniazid is suggested for at least the first 2 months of

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therapy **(BIII)** and perhaps for the continuation phase with rifampin and ethambutol as well **(CIII)**, for a total duration of treatment of 9 months **(BII)**.

The complexity and duration of treatment are substantially increased for TB strains resistant to rifampin alone or to rifampin and other drugs. These patients require treatment with second-line, and perhaps third-line, TB medications that should be selected based on drug-susceptibility testing results, and that are less effective, more toxic, and require 12 to 24 months of treatment.[151] Furthermore, therapy for MDR-TB is rapidly evolving as novel drugs for TB treatment are introduced. Thus, treatment of MDR-TB should involve an expert with experience in treating drug-resistant TB. If a local expert is not available, one option is to contact a CDC Regional Training and Medical Consultation Center at http://www.cdc.gov/tb/education/rtmc/default.htm.

Preventing Recurrence

The risk of recurrent TB in patients with HIV co-infection appears to be somewhat higher than in those who are HIV-uninfected and receiving the same TB treatment regimen in the same setting.[152] 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.[153,154] In settings with low rates of TB (e.g., the United States), recurrent TB due to re-infection is uncommon, even among HIV-infected patients.[155]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV coinfection: 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,[156,157] 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.

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.[158-161] There are only limited data on 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.[162]

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.[163,164] However, the risk of progression from LTBI to active TB in individuals on ART is significantly decreased;[165] therefore, HIV-infected pregnant women should be receiving ART for prevention of mother-to-child transmission. Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[166]

The diagnostic evaluation for TB disease in pregnant women is the same as for non-pregnant adults. Chest

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radiographs with abdominal shielding result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes including preterm birth, low birthweight, and intrauterine growth retardation 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.[158-161,167-170] Congenital TB infection of the infant has been reported, although it appears relatively uncommon.[171] However, in 1 study of 107 women with active TB during pregnancy in South Africa, TB was detected in 16% of neonates (12 by culture and 4 by smear microscopy) sampled within the first 3 weeks of life.[172]

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.[173] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(CIII)**.
- Rifampin is not teratogenic in humans.
- Pyrazinamide is not teratogenic among animals. Experience is limited with use in human pregnancy. Although the World Health Organization and the International Union Against Tuberculosis and Lung Diseases[174,175] 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.[176] 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.
- Ethambutol is teratogenic among rodents and rabbits at doses that are much higher than those used among humans. No evidence of teratogenicity has been observed among humans. Ocular toxicity has been reported among adults taking ethambutol, but changes in visual acuity have not been detected in infants born after exposure *in utero*.

Experience with using the majority of the second-line drugs for TB during pregnancy is limited.[177-180] 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 among pregnant women:

- Streptomycin use has been associated with a 10% rate of eighth 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 *in utero* to quinolones, quinolones are typically not recommended for pregnant women and among 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.[181,182] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[183]
- Para-aminosalicylic acid is not teratogenic among rats or rabbits.[176] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during

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the first trimester.[184] No specific pattern of defects and no increase in rate of defects have been detected among 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 among mice, rats, and rabbits after high-dose exposure; no increased risk for defects was noted with doses similar to those used among humans, but experience is limited with use during human pregnancy. Thus, ethionamide should be avoided unless its use is necessary **(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 (page 1 of 2)

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 mg PO daily **(AII)** *or*
- INH 900 mg PO BIW (by DOT) + pyridoxine 25 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)**
- 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 Table 5 for dosing recommendations of ARV drugs when used with RIF or RFB.

For Drug-Sensitive TB

Intensive Phase (2 Months)

- Daily therapy (5–7 days per week) given as DOT is recommended for all patients during the intensive phase **(AII)**.
- 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) or TIW **(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—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)**
- The total duration of therapy should be based on number of doses received, not on calendar time **(BIII)**.

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)

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- 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 **(BII)**; 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 approximately 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 approximately 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 Table 5 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 nevirapine should be omitted.
- RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving HIV PIs **(BIII)**.
- RPT administered once 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, may consider use of corticosteroid, and 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; BIW = twice weekly; CNS = central nervous system; DOT = directly observed therapy; EMB = ethambutol; INH=isoniazid; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = oral; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; TB = tuberculosis; TIW = thrice weekly; TST = tuberculin skin test; IGRA = interferon-gamma release assays.

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

Drug	Daily	3x/week
Isoniazid	5 mg/kg (usual dose 300 mg)	15 mg/kg (usual dose 900 mg)
Rifampin **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, or EVG/COBI/TDF/FTC	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)
Rifabutin without HIV PIs, EFV, RPV or EVG/COBI/TDF/FTC	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)
with HIV PIs	150 mg[a]	300 mg[a]
with EFV	450–600 mg	450–600 mg
with EVG/COBI/TDF/FTC	150 mg[b]	150 mg[b]
Pyrazinamide (weight-based dosing)		
40–55 kg	1000 mg (18.2–25.0 mg/kg)	1500 mg (27.3–37.5 mg/kg)
56–75 kg	1500 mg (20.0–26.8 mg/kg)	2500 mg (33.3–44.6 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)	3000 mg (33.3–39.5 mg/kg)
>90 kg	2000 mg[c]	3000 mg[c]
Ethambutol (weight-based dosing)		
40–55 kg	800 mg (14.5–20.0 mg/kg)	1200 mg (21.8–30.0 mg/kg)
56–75 kg	1200 mg (16.0–21.4 mg/kg)	2000 mg (26.7–35.7 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)	2400 mg (26.7–31.6 mg/kg)
>90 kg	1600 mg[c]	2400 mg[c]

[a] 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.

[b] Avoid co-administration of EVG/COBI/TDF/FTC with rifabutin, if possible. If used together, consider therapeutic drug monitoring 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; TDF = tenofovir disoproxil fumarate

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

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.

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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)**.

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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

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(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)**.

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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.

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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

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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.

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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

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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

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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]

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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.

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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

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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

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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

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- 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.

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- 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

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Bacterial Enteric Infections (Last updated May 3, 2016; last reviewed May 3, 2016)

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.

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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

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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

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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

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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)**.

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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.

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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.

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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)**

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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.

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Bartonellosis (Last updated May 7, 2013; last reviewed May 7, 2013)

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.

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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)**.

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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)**.

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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

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Syphilis (Last updated December 17, 2015; last reviewed December 17, 2015)

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

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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

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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

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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

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(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.

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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

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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

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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.

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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

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Mucocutaneous Candidiasis (Last updated December 8, 2015; last reviewed December 8, 2015)

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

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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

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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

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(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

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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)**

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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

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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 August 17, 2016)

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

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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

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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,

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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,

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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

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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

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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*
- Remains asymptomatic from cryptococcal infection, *and*

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Recommendations for Preventing and Treating Cryptococcosis (page 2 of 2)

- 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 Cryptococcosis 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

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Histoplasmosis (Last updated May 7, 2013; last reviewed May 7, 2013)

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.

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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

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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)**.

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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

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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

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Coccidioidomycosis (Last updated November 10, 2016; last reviewed November 10, 2016)

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

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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

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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.

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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

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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 Coccidioidomycosis (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.

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Recommendations for Treating Coccidioidomycosis (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

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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.

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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]

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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

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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

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(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.

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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)**.

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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

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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)**.

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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)**.

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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

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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,

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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

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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.

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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.

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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

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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.

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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

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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

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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)**.

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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.

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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

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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

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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-

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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]

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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

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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

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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)

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- 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.

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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.

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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

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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

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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.

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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

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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.

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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.

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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)**

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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

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Hepatitis B Virus Infection (Last updated April 22, 2015; last reviewed April 22, 2015)

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]

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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

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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

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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

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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.

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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,

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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

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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

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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.

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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)**.

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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

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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-

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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

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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

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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.

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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

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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

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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]

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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,

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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.

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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.

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Malaria (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. In 2006, the World Health Organization estimated that out of a global population of 6.6 billion, 1.2 billion individuals live in areas where malaria is highly endemic (defined as 1 or more cases per 1,000 people per year) and 2.1 billion individuals live in areas of some risk of malaria transmission.[1] Of the nearly 250 million cases of malaria worldwide in 2006 (based on reports and models), between 152 million and 287 million occurred in Africa, the area of the world with the highest HIV prevalence.[1] The global case-fatality rate was 4 deaths/10,000 infections per year, with ~90% of deaths occurring in Africa and 85% of those deaths in children younger than 5 years of age. Current attributable morbidity and mortality likely is an underestimate, 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 the 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, 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

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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 too.[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 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

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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 macrophages[38] and increased viral load,[39] raising the possibility of placental malaria leading to increased mother-to-child transmission (MTCT) of HIV. However, data are conflicting concerning the effect of malaria during pregnancy on risk of MTCT. One study in Uganda demonstrated increased MTCT in women with placental malaria,[40] but studies from Kenya did not demonstrate this association.[41,42]

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.

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 Centers for Disease Control and Prevention (CDC)'s malaria website (http://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-

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infected and are available at CDC's malaria website **(AIII)** (http://www.cdc.gov/malaria).

Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.[43] 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.[44] 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 and the species of *Plasmodium* identified, 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 (http://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 Antiretroviral Therapy (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 (see Table 5). Several potential drug interactions can occur between antimalarial and HIV drugs.[45] Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at 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; conversely, nevirapine and efavirenz can reduce plasma quinine levels. Potential interactions can occur between ritonavir 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,[46] but data are lacking in HIV-infected adults. 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

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neutropenia in those on ART, particularly zidovudine, which was attributed to the amodiaquine component of therapy.[47]

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors have the potential to affect metabolism of artemisinin-containing drugs,[48] 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.[49] 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.[50] 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.[51] For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with quinine for 7 days is recommended. For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended.

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.[51,52] 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.[53] 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.[52] 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.

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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: http://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
  - The CDC malaria website: http://www.cdc.gov/malaria/
  - 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

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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

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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.

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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)**.

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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

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Leishmaniasis (Last updated May 9, 2014; last reviewed May 7, 2013)

Epidemiology

Leishmaniasis is caused by obligate intracellular protozoa that survive and replicate in intracellular 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 1.5 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 has 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] In a study in a treatment center in Humera in northwestern Ethiopia, 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, leading to 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, and 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* 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, relying on mechanical transfer of amastigotes via syringe.[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%–100%), systemic malaise (70%–90%), splenomegaly (usually moderate) (60%–90%), hepatomegaly without splenomegaly (34%–85%), hepatosplenomegaly (68%–73%), lymphadenopathy (12%–57%), and pancytopenia (50%–80%).[5,15] Anemia is usually marked, with <10g hemoglobin/dL (49%–100%); leukopenia moderate, with <2400 leukocytes/µL (56%–95%); and thrombocytopenia usually is present

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(52%–93%). Splenomegaly is less pronounced in HIV-co-infected patients than in immunocompetent patients with visceral leishmaniasis.[15] In those 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. Other methods useful for demonstrating *Leishmania* in the blood or tissue of co-infected patients include detection of *Leishmania* nucleic acid by PCR amplification (>95% sensitivity).[18]

Serologic tests to detect antibodies against *Leishmania* antigens have high sensitivity 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 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 in injection-drug users, such as the use of needle exchange programs, are appropriate.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended, and no screening or preemptive

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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 include oral miltefosine and parenteral paromomycin. Miltefosine is an oral antileishmanial agent currently available outside the United States and may be used under individual investigational new drug protocols in the United States. Consultations and drug requests should be addressed to CDC Parasitic Diseases Inquiries (404-718-4745; parasites@cdc.gov), the CDC Drug Service (404-639-3670), and; for emergencies after business hours, on weekends, and federal holidays; through the CDC Emergency Operations Center (770-488-7100).

Cure rates for visceral leishmaniasis in HIV-negative patients are reported to be approximately 95%.[44] In Ethiopia, HIV-co-infected patients treated with miltefosine had lower initial cure rates, compared with those treated with pentavalent antimony (sodium stibogluconate) (78% vs. 90%), but also lower mortality.[45] The adult dose is 100 mg daily for 4 weeks. Data supporting the use of miltefosine in HIV-co-infected patients are limited, but it can be used for treatment of visceral leishmaniasis in Europe under a compassionate use protocol **(CIII)**.[46] Gastrointestinal symptoms are common but they rarely limit treatment. Paromomycin, an aminoglycoside which is available outside the United States, has been shown to be used successfully in a small number of HIV-negative visceral leishmaniasis patients in India and is now in use in several countries.[40] No efficacy data currently are available for paromomycin in HIV-co-infected patients. A recent trial of combination therapy (liposomal amphotericin plus miltefosine or paromomycin; miltefosine plus paromomycin) produced promising results in patients in India whose visceral leishmaniasis was not severe.[47] Further research is needed to validate the efficacy of these regimens in severe disease in visceral leishmaniasis in other 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

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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 decreases 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 over an hour before 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 vigilance 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 the 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 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]

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Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of anti-leishmanial 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, it has been suggested as another alternative for secondary prophylaxis in a dosage of 6 mg/kg IV every 2 to 4 weeks **(CIII)**.[66] Allopurinol, in a dose of 300 mg orally 3 times daily, used for maintenance therapy 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 are so little 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 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)**. 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.

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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; drugservice@cdc.gov; for emergencies, call 770-488-7100)
- Miltefosine 100 mg PO daily for 4 weeks **(CIII)**. Requires individual IND; consultation should be addressed to CDC Parasitic Diseases Inquiries (404-718-4745; parasites@cdc.gov) or the CDC Drug Service (404-639-3670; drugservice@cdc.gov; for emergencies, call 770-488-7100)

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 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 = the Centers for Disease Control and Prevention; IM = intramuscular; IND = investigational new drug; IV = intravenous

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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

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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]

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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

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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]

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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

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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.

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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]

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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]

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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

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Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 1 of 5)
(Last updated December 10, 2015; last reviewed December 10, 2015)

Opportunistic Infections	Indication	Preferred	Alternative
***Pneumocystis* pneumonia (PCP)**	• CD4 count <200 cells/mm³ **(AI)**, *or* • Oropharyngeal candidiasis **(AII)**, *or* • CD4 <14% **(BII)**, *or* • History of AIDS-defining illness **(BII)**, *or* • CD4 count >200 but <250 cells/mm³ 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[c], 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 mg) PO daily x 9 months **(AII)**, *or* • INH 900 mg PO BIW (by DOT) + pyridoxine 25 mg PO daily x 9 months **(BII)**.	• Rifampin 600 mg PO daily x 4 months **(BIII)**, *or* • Rifabutin (dose adjusted based on concomitant ART)[d] x 4 months **(BIII)**. For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities **(AII)**.
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)[d] **(BI)**; rule out active TB before starting rifabutin

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Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 2 of 5)

Opportunistic Infections	Indication	Preferred	Alternative
***Streptococcus pneumoniae* infection**	For individuals who have not received any pneumococcal vaccine, regardless of CD4 count, followed by:	PCV13 0.5 mL IM x 1 **(AI)**.	PPV23 0.5 mL IM or SQ x 1 **(BII)**
	• if CD4 count ≥200 cells/μL	PPV23 0.5 mL IM or SQ at least 8 weeks after the PCV13 vaccine **(AII)**.	
	• if CD4 count <200 cells/μL	PPV23 can be offered at least 8 weeks after receiving PCV13 **(CIII)** or can wait until CD4 count increased to ≥200 cells/μL **(BIII)**.	
	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 • 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 **contraindicated** 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)** – **not recommended** 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)**	

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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)**	

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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/.	

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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 Table 5 for dosing recommendation

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.

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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 November 10, 2016; last reviewed November 10, 2016)

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)**.

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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).**

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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)**.

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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) or TIW **(AIII)** Total Duration of Therapy (For Drug-Susceptible TB): • Pulmonary 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. RIF **is not recommended** for patients receiving HIV PI because of its induction of PI metabolism **(AII)**. RFB is a less potent CYP3A4 inducer than RIF and is preferred in patients receiving PIs. Once weekly rifapentine can result in development of rifamycin resistance in HIV-infected patients and **is not recommended (AI)**. 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.

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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)**.
	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)**.
			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.

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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)**.		

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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)**	

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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.

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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)**.

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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.

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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)**

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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)**.

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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)**.

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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 300mg 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.

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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)**.

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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.

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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)**.

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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.

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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).

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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.

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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.

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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.

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Table 3. Recommended Doses of First-Line Drugs for Treatment of Tuberculosis in Adults and Adolescents (Last updated May 7, 2013; last reviewed May 7, 2013)

Drug	Daily	3x/week
Isoniazid	5 mg/kg (usual dose 300 mg)	15 mg/kg (usual dose 900 mg)
Rifampin **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, or EVG/COBI/TDF/FTC	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)
Rifabutin without HIV PIs, EFV, RPV, or EVG/COBI/TDF/FTC	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)
with HIV PIs	150 mg[a]	300 mg[a]
with EFV	450–600 mg	450–600 mg
with EVG/COBI/TDF/FTC	150 mg[b]	150 mg[b]
Pyrazinamide (weight-based dosing) 40–55 kg	1000 mg (18.2–25.0 mg/kg)	1500 mg (27.3–37.5 mg/kg)
56–75 kg	1500 mg (20.0–26.8 mg/kg)	2500 mg (33.3–44.6 mg/kg)
76–90 kg	2000 mg (22.2–26.3 mg/kg)	3000 mg (33.3–39.5 mg/kg)
>90 kg	2000 mg[c]	3000 mg[c]
Ethambutol (weight-based dosing) 40–55 kg	800 mg (14.5–20.0 mg/kg)	1200 mg (21.8–30.0 mg/kg)
56–75 kg	1200 mg (16.0–21.4 mg/kg)	2000 mg (26.7–35.7 mg/kg)
76–90 kg	1600 mg (17.8–21.1 mg/kg)	2400 mg (26.7–31.6 mg/kg)
>90 kg	1600 mg[c]	2400 mg[c]

[a] 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.

[b] Avoid co-administration of EVG/COBI/TDF/FTC with rifabutin, if possible. If used together, consider therapeutic drug monitoring 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; TDF = tenofovir disoproxil fumarate

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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

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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

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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.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 1 of 14) (Last updated May 7, 2013; last reviewed May 7, 2013)

This table provides clinicians with information regarding known or suspected pharmacokinetic interactions between drugs commonly used for treatment or prevention of HIV-associated opportunistic infections or for treatment of HIV infection. Note that there may be substantial inter-patient variability in the magnitude of the interactions. Moreover, the table only provides suspected interactions between 2 drugs when used in combination, but cannot be used to predict the interaction potential when three or more drugs with similar metabolic pathways are co-administered. In these cases, alternative options with less drug interaction potential or therapeutic drug monitoring (if available), should be considered.

Throughout the table, two recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The definitions for these terms used in the Recommendations column are summarized below:

Co-administration should be avoided.

Indicates there is strong evidence or likelihood that the drug-drug interaction will result in either

1) Markedly decreased concentrations of one or both drugs, which may render one or both drugs ineffective, or

2) Increased concentrations of one or both drugs, which may result in excessive risk of toxicity that cannot be managed with a dose modification of one or both drugs.

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 reasonable options that provide a more favorable risk-benefit assessment. In some instances, a suggested strategy is provided with the recommendation based upon available knowledge and alternatives. If other more favorable options exist, the clinician is advised to consider changing components of the regimen to accommodate a more effective and/or safer regimen.

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether-Lumefantrine	Darunavir/ritonavir	Artemether AUC ↓ 16%; DHA AUC ↓ 18%; lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. Monitor for anti-malarial efficacy and lumefantrine toxicities.
	Efavirenz	Artemether AUC ↓ 79%; DHA AUC ↓ 75%; lumefantrine AUC ↓ 56%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy.
	Etravirine	Artemether AUC ↓ 38%; DHA AUC ↓ 15%; lumefantrine AUC ↓ 13%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy.
	Lopinavir/ritonavir	Artemether AUC ↓ 40%; DHA AUC ↓ 17%; lumefantrine AUC ↑ 470%	Data based on single dose study. Clinical significance unknown. Monitor for anti-malarial efficacy and lumefantrine toxicities.
	Nevirapine	Artemether AUC ↓ 72%; DHA AUC ↓ 37%; lumefantrine (no difference in one study, but AUC ↑ 55.6% in another study)	Clinical significance unknown. Monitor for anti-malarial efficacy.
	Rifampin	Artemether AUC ↓ 89%; DHA AUC ↓ 85%; lumefantrine AUC ↓ 68%	Co-administration should be avoided.
Atovaquone	Atazanavir/ritonavir	Atovaquone AUC ↓ 46%; no data with unboosted atazanavir (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between boosted or unboosted atazanavir and atovaquone suspension)	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 2 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Atovaquone, continued	Doxycycline	Atovaquone concentrations ↓ 40% with tetracycline; interaction study with doxycycline not available	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.
	Efavirenz	Atovaquone AUC ↓ 75% (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between efavirenz and atovaquone suspension)	Co-administration should be avoided if possible. If co-administered, monitor for decreased atovaquone efficacy.
	Lopinavir/ritonavir	Atovaquone AUC ↓ 74% (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between lopinavir/ritonavir and atovaquone suspension)	Co-administration should be avoided if possible. If co-administered, monitor for decreased atovaquone efficacy.
	Rifabutin	Atovaquone AUC ↓ 34%; rifabutin AUC ↓ 19%	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.
	Rifampin	Atovaquone concentrations ↓ 52%; rifampin concentrations ↑ 37%	Co-administration should be avoided.
	Zidovudine	Zidovudine AUC ↑ 31%	No dose adjustment necessary; monitor for zidovudine-associated toxicities.
Boceprevir	Atazanavir/ritonavir	Boceprevir AUC no change; atazanavir AUC ↓ 35%, C_{min} ↓ 49%; ritonavir AUC ↓ 36%	Co-administration should be avoided.
	Clarithromycin	May ↑ concentrations of clarithromycin	No dose adjustment necessary in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Darunavir/ritonavir	Boceprevir AUC ↓ 32%, C_{min} ↓ 35%; darunavir AUC ↓ 44%, C_{min} ↓ 59%; ritonavir AUC ↓ 27%	Co-administration should be avoided.
	Efavirenz	Boceprevir AUC ↓ 19%, C_{min} ↓ 44%; efavirenz AUC ↑ 20%	Significance unknown; co-administration should be avoided.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	No PK data, bi-directional interaction possible	Co-administration should be avoided.
	Etravirine	Boceprevir AUC ↑ 10%, C_{min} ↓12%; etravirine AUC ↓ 23%, C_{min} ↓ 29%	Clinical significance of this interaction is unknown.
	Itraconazole, ketoconazole, posaconazole, voriconazole	Boceprevir AUC ↑ 230% when co-administered with ketoconazole 400 mg bid. Concentrations of azoles may be ↑	Doses of ketoconazole and itraconazole should not exceed 200 mg/day. Consider monitoring azole drug concentrations and adjust dose accordingly. Monitor for boceprevir-associated toxicities.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 3 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Boceprevir, continued	Lopinavir/ritonavir	Boceprevir AUC ↓ 45%, C_{min} ↓ 57%; lopinavir AUC ↓ 34%, C_{min} ↓ 43%; ritonavir AUC ↓ 22%	Co-administration should be avoided.
	Raltegravir	No significant interaction.	This combination can be co-administered without dosage adjustment
	Rifabutin	↑ in rifabutin concentrations are anticipated, while exposure of boceprevir may be ↓	Co-administration should be avoided, if possible. If used in combination, consider monitoring rifabutin concentration and adjust dose accordingly.
	Rifampin	No PK data. Significant ↓ in boceprevir exposure is anticipated.	Co-administration should be avoided.
Caspofungin	Efavirenz, nevirapine	Possible ↓ in caspofungin concentrations based on regression analyses of patient PK data. No formal PK study available.	Manufacturer recommends consider increasing maintenance dose of caspofungin to 70 mg/day when co-administered with CYP450 inducers.
	Rifampin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
Clarithromycin	Atazanavir	Atazanavir C_{min} ↑ 91%, AUC ↑ 28%; clarithromycin AUC ↑ 94%, C_{min} ↑ 160% Co-administration with atazanavir/ritonavir has not been studied.	Because of concerns for QTc prolongation when these drugs are used in combination, reduce clarithromycin dose by 50% or switch to azithromycin.
	Boceprevir	Concentrations of clarithromycin may be ↑	No dose adjustment in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Darunavir/ritonavir	Clarithromycin AUC ↑ 57%, C_{min} ↑ 174%	No dose adjustment in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Efavirenz	Clarithromycin AUC ↓ 39%	Significance unknown; consider switching to azithromycin.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Clarithromycin, cobicistat, and elvitegravir concentrations may be increased.	CrCl > 60 mL/min: no dosage adjustment. CrCl 50–60 mL/min: reduce clarithromycin dose by 50%. To avoid drug interaction, consider switching to azithromycin.
	Etravirine	Clarithromycin AUC ↓ 39%; etravirine C_{min} ↑ 46%, AUC ↑ 42%	Significance unknown; consider switching to azithromycin.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 4 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Clarithromycin, continued	Fluconazole	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function.
	Itraconazole	Possible bi-directional CYP3A4 inhibition and increased exposure of both drugs.	Monitor for toxicities of both itraconazole and clarithromycin, consider monitoring drug concentrations and adjust dose accordingly, or consider switching to azithromycin.
	Lopinavir/ritonavir	Increased clarithromycin exposure expected.	No dose adjustment necessary in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Maraviroc	Potential for inhibition of maraviroc metabolism and ↑ maraviroc concentration.	Decrease maraviroc dose to 150 mg BID or switch to azithromycin.
	Nevirapine	Clarithromycin AUC ↓ 29%, C_{min} ↓ 46%	Co-administration should be avoided if possible; consider switching to azithromycin.
	Rifabutin	Clarithromycin AUC ↓ by 44%; rifabutin AUC ↑ 76%–99%.	Consider reducing rifabutin dose, monitor for rifabutin-associated toxicities, Consider monitoring serum concentration and adjust dose accordingly; or switch to azithromycin.
	Rifampin	Mean clarithromycin concentration ↓ 87%	This combination should be avoided. Switch to azithromycin.
	Saquinavir	Saquinavir C_{max} ↑ 187%, AUC ↑ 177%; clarithromycin C_{max} and AUC ↑ 40% (studied with saquinavir 1200 mg TID) Clarithromycin has not been studied with ritonavir-boosted saquinavir.	No dose adjustment necessary in patients with normal renal function. Clarithromycin dose adjustment may be necessary in patients with renal dysfunction. Monitor closely because of additive risk of QTc prolongation associated with increased concentrations of both drugs. Consider switching to azithromycin.
	Telaprevir	Concentrations of both telaprevir and clarithromycin may be increased during co-administration.	Use with caution and monitor for adverse events, including QT prolongation. Reduce clarithromycin dose during concomitant use with telaprevir in patients with impaired renal function. Consider switching to azithromycin.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 5 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Clarithromycin, continued	Tipranavir/ritonavir	Clarithromycin AUC ↑ 19%, C_{min} ↑ 68%; tipranavir AUC ↑ 66%, C_{min} ↑ 100%	Monitor for tipranavir-associated toxicities. No dose adjustment necessary in patients with normal renal function. Clarithromycin dose adjustment may be necessary in patients with renal dysfunction. Consider switching to azithromycin.
Dapsone	Rifampin	Dapsone concentrations ↓ 7 to 10-fold and half-life ($t_{1/2}$) ↓ from 24 to 11 hours.	Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
Doxycycline	Atovaquone	Atovaquone concentrations ↓ by approximately 40% with tetracycline; interaction study with doxycycline not available.	Until doxycycline-atovaquone interaction data become available, avoid this combination if possible.
	Rifampin	Doxycycline AUC ↓ by 59%	Potential for decreased doxycycline efficacy; monitor closely for therapeutic failure.
Erythromycin	Itraconazole	Itraconazole C_{max} ↑ 44%, AUC ↑ 36%. Potential for ↑ in erythromycin concentration.	Monitor for toxicities of both drugs, potential for QT prolongation; monitor itraconazole concentrations and adjust dose accordingly, or consider alternative azole or macrolide.
	Telaprevir	Concentrations of telaprevir and erythromycin may ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation.
Fluconazole	Clarithromycin	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function.
	Efavirenz	Efavirenz AUC ↑ 16%; no change in fluconazole AUC.	No dose adjustment necessary.
	Etravirine	Etravirine AUC ↑ 86%, C_{min} ↑ 109%	Co-administer with caution. Monitor for etravirine-associated toxicities.
	Nevirapine	Nevirapine concentrations ↑ 100% (compared with historic control).	Co-administration should be avoided, if possible. If co-administered, monitor for nevirapine-associated toxicities.
	Rifabutin	Rifabutin AUC ↑ 80%; no effect on fluconazole exposure.	Monitor for rifabutin-associated toxicities; consider monitoring rifabutin concentrations; may need to reduce rifabutin dose to 150 mg/day.
	Rifampin	Fluconazole AUC ↓ 23%–56%; no change in rifampin exposure.	Monitor for antifungal efficacy; may need to increase fluconazole dose.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 6 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Fluconazole, continued	Saquinavir	Saquinavir C_{max} ↑ 56%, AUC ↑ 50% (studied with saquinavir 1200 mg TID). Fluconazole has not been studied with ritonavir-boosted saquinavir.	Significance unknown. No dosage adjustment needed.
	Tipranavir/ritonavir	Tipranavir AUC ↑ 50%, C_{min} ↑ 69%	Monitor for tipranavir-associated toxicities; fluconazole doses >200 mg/day not recommended.
	Zidovudine	Fluconazole ↓ glucuronidation of zidovudine; fluconazole 400 mg/day results in zidovudine AUC ↑ 74%	Monitor for zidovudine-associated toxicities.
Itraconazole	Boceprevir	Concentrations of itraconazole and/or boceprevir may be ↑	Itraconazole dose should not exceed 200 mg/day. Monitor itraconazole concentration and adjust dose accordingly.
	Clarithromycin	Possible bi-directional CYP3A4 inhibition and ↑ exposure of both drugs.	Monitor for toxicities of both itraconazole and clarithromycin. Monitor itraconazole concentration and adjust dose accordingly. Alternatively, consider switching to azithromycin.
	Efavirenz	Itraconazole AUC ↓ 39%, C_{min} ↓ 44% in PK studies; No change to efavirenz AUC. Failure to achieve therapeutic itraconazole concentrations has been reported.	Co-administration should be avoided if possible. If used in combination, monitor itraconazole concentrations and adjust dose accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat, elvitegravir, and itraconazole serum concentration may be ↑	Avoid itraconazole >200 mg/day. Monitor itraconazole serum concentrations with co-administration.
	Erythromycin	Potential for bi-directional inhibition of metabolism and ↑ serum concentrations of both drugs.	Monitor for toxicities of both drugs, potential for QT prolongation; monitor itraconazole concentrations and adjust dose accordingly, or consider alternative azole or macrolide.
	Etravirine	Etravirine concentration may be ↑; Itraconazole concentration may be ↓. Extent of the interaction unknown.	Dose adjustment with itraconazole may be necessary depending on the presence of other concomitant ARV drugs (e.g., PIs). Monitor itraconazole concentrations and adjust dose accordingly.
	Maraviroc	Potential for inhibition of maraviroc metabolism and ↑ in maraviroc concentration.	Decrease maraviroc dose to 150 mg twice daily.
	Micafungin	Itraconazole AUC ↑ 22%	No dose adjustment necessary.
	Nevirapine	Itraconazole C_{max} ↓ 38%, AUC ↓ 61%; nevirapine: no change	Monitor itraconazole concentrations and adjust accordingly dose; monitor therapeutic efficacy.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 7 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Itraconazole, continued	PIs	Potential for bi-directional CYP3A4 inhibition with ↑ exposure of both drugs.	Monitor for PI-associated toxicities; monitor itraconazole concentrations and itraconazole-associated toxicities
	Rifabutin	Itraconazole AUC ↓ 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin exposure.	Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole concentrations and adjust dose accordingly; monitor for rifabutin-associated toxicities and consider monitoring rifabutin concentrations.
	Rifampin	Itraconazole AUC ↓ 64%–88%; no change in rifampin concentrations.	Co-administration should be avoided. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rilpivirine	Potential ↑ in rilpivirine exposure or ↓ in itraconazole.	No dose adjustment for rilpivirine; monitor for rilpivirine-associated toxicities. Consider monitoring itraconazole concentration and adjust dose as necessary.
	Telaprevir	Concentrations of itraconazole and telaprevir may be ↑	If co-administration is necessary, high doses of itraconazole (>200 mg/day) are not recommended. Monitor for toxicities to both drugs. Consider monitoring itraconazole concentration and adjust dose accordingly.
Mefloquine	Rifampin	Mefloquine AUC ↓ 68%.	Co-administration should be avoided, if possible. Use alternative anti-malarial drug or rifabutin.
	Ritonavir	When studied with ritonavir 200 mg twice daily—ritonavir AUC ↓ 31%, C_{min} ↓ 43%; no substantial change in mefloquine PK. Effect on exposure of ritonavir-boosted PIs unknown.	Use mefloquine with caution with PIs.
Micafungin	Itraconazole	Itraconazole AUC ↑ 22%	No dose adjustment necessary.
Posaconazole	Atazanavir (+/- ritonavir)	With unboosted-atazanavir—atazanavir AUC ↑ 268%; with ritonavir-boosted atazanavir—atazanavir AUC ↑ 146%	Co-administration should be avoided, if possible; or monitor atazanavir concentrations and adjust doses accordingly; monitor for atazanavir-associated toxicities.
	Boceprevir	Posaconazole concentration may be ↑	Use with caution, considering monitoring posaconazole concentration and adjust dose accordingly.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 8 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Posaconazole, continued	Efavirenz	Posaconazole AUC ↓ 50%, C_{max} ↓ 45%	Co-administration should be avoided, if possible; or monitor posaconazole concentrations and adjust doses accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat, elvitegravir, and posaconazole concentrations may be ↑	Monitor posaconazole concentration and adjust dose accordingly.
	Etravirine	Etravirine exposure may be ↑; posaconazole exposure unlikely to be affected.	No dose adjustment necessary; monitor for etravirine-associated toxicities.
	Fosamprenavir	Amprenavir AUC ↓ 65%; posaconazole AUC ↓ 23% (studied without ritonavir boosting). No data for fosamprenavir/ritonavir.	Co-administration should be avoided, or monitor drug concentrations and adjust doses accordingly.
	Rifabutin	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%.	Co-administration should be avoided, if possible, or monitor posaconazole and rifabutin concentrations and adjust doses accordingly; monitor clinical response.
	Rifampin	Posaconazole exposure may be ↓ significantly.	Co-administration should be avoided, if possible. If used, monitor posaconazole concentrations and adjust dose accordingly.
	Rilpivirine	Potential ↑ in rilpivirine concentrations.	Monitor for rilpivirine-associated toxicities.
	Ritonavir	Ritonavir AUC ↑ 80%, C_{max} ↑ 49%	No ritonavir dose adjustment necessary.
	Telaprevir	Concentrations of posaconazole and telaprevir may be ↑	Use with caution with increased monitoring for posaconazole- or telaprevir-associated toxicities, including QT prolongation. Consider monitoring posaconazole level and adjust dose accordingly.
Proguanil	Atazanavir/ritonavir	Proguanil AUC ↓ 41%; no data with unboosted atazanavir.	Use with caution.
	Efavirenz	Proguanil AUC ↓ 43%	Use with caution.
	Lopinavir/ritonavir	Proguanil AUC ↓ 38%	Use with caution.
Ribavirin	Didanosine	↑ intracellular concentrations of ddA-TP	↑ serious didanosine-associated mitochondrial toxicities. Co-administration should be avoided.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 9 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifabutin	Atovaquone	Atovaquone AUC ↓ 34%; rifabutin AUC ↓ 19%.	Co-administration should be avoided. If used, monitor for therapeutic response.
	Boceprevir	↑ in rifabutin concentrations are anticipated, while exposure of boceprevir may be ↓	Co-administration should be avoided, if possible. If used in combination, consider monitoring rifabutin concentration and adjust dose accordingly.
	Clarithromycin	Clarithromycin AUC ↓ 44%; rifabutin AUC ↑ 76%–99%.	Consider reducing rifabutin dose, monitor for rifabutin-associated toxicities, Consider monitoring serum concentration and adjust dose accordingly; or switch to azithromycin.
	Efavirenz	Rifabutin AUC ↓ 38%; no change in efavirenz exposure.	Increase rifabutin dose to 450–600 mg/day; effect of efavirenz + PI(s) on rifabutin concentrations has not been studied.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Elvitegravir AUC ↓ 21%, C_{min} ↓ 67%; rifabutin active metabolite (25-O-desacetyl rifabutin) AUC ↑ 625%	Co-administration should be avoided, if possible. Consider using alternative antimycobacterial agent or alternative ARV drug. If used, consider rifabutin 150 mg once daily or every other day, consider monitoring rifabutin concentrations and adjust dose accordingly.
	Etravirine	Etravirine C_{min} ↓ 35% and AUC ↓ 37%; rifabutin AUC ↓ 17%.	Use standard rifabutin dose of 300 mg daily if not used with a ritonavir-boosted PI. In patients receiving a ritonavir-boosted PI, consider alternative agents if possible, or use serum concentration to guide dosing of rifabutin.
	Fluconazole	Rifabutin AUC ↑ 80%; no effect on fluconazole exposure.	Monitor for rifabutin toxicity and consider monitoring rifabutin concentrations and adjust dose accordingly; may need to reduce rifabutin dose to 150 mg/day.
	Itraconazole	Itraconazole AUC ↓ 70%; potential for ↑ rifabutin exposure.	Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole and rifabutin concentrations and adjust doses accordingly. Monitor for rifabutin-associated toxicities.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 10 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifabutin, continued	Maraviroc	Concentration of maraviroc may be ↓	If used without another strong CYP3A4 inducer or inhibitor, maraviroc 300 mg BID. If used with a strong CYP3A4 inhibitor, use maraviroc 150 mg BID.
	Nevirapine	Rifabutin AUC ↑ 17%, 25-O-desacetyl rifabutin AUC ↑ 24%; nevirapine C_{min} ↓ 16%.	No dose adjustment necessary.
	PI boosted by ritonavir	Significant ↑ in rifabutin concentrations.	Use rifabutin 150 mg daily or 300 mg 3 times/week. Consider monitoring rifabutin concentrations and adjust dose accordingly.
	Posaconazole	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%.	Co-administration should be avoided, if possible, or monitor posaconazole and rifabutin concentrations and adjust doses accordingly; monitor clinical response.
	Rilpivirine	Rilpivirine AUC ↓ 46%	Co-administration should be avoided.
	Telaprevir	Concentrations of telaprevir may be ↓, while rifabutin concentrations may be ↑	Co-administration should be avoided.
	Voriconazole	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 3-fold.	Co-administration should be avoided, if possible. If used in combination, monitor voriconazole and rifabutin concentrations and adjust dose accordingly. Monitor for clinical responses and toxicities.
Rifampin	Artemether/ lumefantrine	Artemether AUC ↓ 89%; DHA AUC ↓ 85%; lumefantrine AUC ↓ 68%	Co-administration should be avoided.
	Atovaquone	Atovaquone concentrations ↓ 52%; rifampin concentrations ↑ 37%	Co-administration should be avoided.
	Boceprevir	No PK data. Significant ↓ in boceprevir exposure is anticipated.	Co-administration should be avoided.
	Caspofungin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
	Clarithromycin	Mean clarithromycin concentrations ↓ 87%	This combination should be avoided; consider switching to azithromycin.
	Dapsone	Dapsone concentrations ↓ 7- to 10-fold and half-life ($t_{1/2}$) ↓ from 24 to 11 hours.	Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
	Doxycycline	Doxycycline AUC ↓ by 59%	Potential for decreased doxycycline efficacy; monitor closely for therapeutic failure.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 11 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifampin, continued	Efavirenz	Efavirenz AUC ↓ 22%, C_{min} ↓ 25%; no change in rifampin exposure.	Maintain efavirenz dose at 600 mg once daily and monitor for virologic response. Some clinicians suggest increasing efavirenz dose to 800 mg per day in patients >60 kg.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat and elvitegravir concentrations may be significantly ↓	Co-administration should be avoided. Consider an alternative antimycobacterial agent or alternative antiretroviral drug regimen.
	Etravirine	Potential significant ↓ in etravirine concentration.	Co-administration should be avoided.
	Fluconazole	Fluconazole AUC ↓ by 23%–56%; no change in rifampin exposure.	Monitor for antifungal efficacy, may need to increase fluconazole dose.
	Itraconazole	Itraconazole AUC ↓ 64%–88%; no change in rifampin concentrations.	Co-administration should be avoided. Consider alternative antifungal and/or antimycobacterial agent(s).
	Maraviroc	Maraviroc AUC ↓ 63%, C_{min} decreased 67%	Increase maraviroc dose to 600 mg twice daily or use alternative antimycobacterial agent.
	Nevirapine	Nevirapine AUC ↓ by >50%, C_{min} ↓ 21-37%; no change in rifampin concentrations.	This combination should be avoided if possible. If adding nevirapine to rifampin is necessary, initiate nevirapine at 200 mg twice daily (i.e., no lead-in period). Do not use nevirapine extended-release formulation.
	Posaconazole	Posaconazole concentrations may be ↓ significantly.	Co-administration should be avoided if possible. If used, monitor posaconazole concentrations and adjust dose if necessary.
	PI (+/- ritonavir-boosting)	Significantly ↓ PI exposure (>75%) despite ritonavir boosting	Co-administration should be avoided.
	Raltegravir	Raltegravir AUC ↓ 40%, C_{min} ↓ 60%	Increase raltegravir dose to 800 mg PO twice daily, monitor for antiretroviral efficacy, or switch to rifabutin.
	Rilpivirine	Rilpivirine AUC ↓ 80%	Co-administration should be avoided.
	Telaprevir	Telaprevir AUC ↓ 92%	Co-administration should be avoided.
	Voriconazole	Voriconazole AUC ↓ 96%	Co-administration should be avoided.
	Zidovudine	Zidovudine AUC ↓ 48%	Monitor for zidovudine efficacy.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 12 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Telaprevir	Atazanavir/ritonavir	Telaprevir AUC ↓ 20%, C_{min} ↓ 15%; atazanavir C_{min} ↑ 85%	No dosage adjustment necessary.
	Clarithromycin	Concentrations of telaprevir and clarithromycin may be ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation. Reduce clarithromycin dose during concomitant use with telaprevir in patients with impaired renal function. Consider switching to azithromycin.
	Darunavir/ritonavir	Telaprevir AUC ↓ 35%, C_{min} ↓ 32%; darunavir AUC and C_{min} ↓ 40%.	Co-administration should be avoided.
	Efavirenz	Telaprevir AUC ↓ 26%; C_{min} ↓ 47%	Increase telaprevir dose to 1125 mg every 8 hours.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	No data. Potential for bi-directional interactions.	Co-administration should be avoided.
	Erythromycin	Concentrations of telaprevir and erythromycin may be ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation.
	Fosamprenavir/ ritonavir	Telaprevir AUC ↓ 32%, C_{min} ↓ 30%; amprenavir AUC ↓ 47%, C_{min} ↓ 56%	Co-administration should be avoided.
	Itraconazole	Concentrations of itraconazole and telaprevir may be ↑	If co-administration is necessary, high doses of itraconazole (>200 mg/day) are not recommended. Monitor for toxicities to both drugs. Consider monitoring itraconazole concentration and adjust dose accordingly.
	Lopinavir/ritonavir	Telaprevir AUC ↓ 54%, C_{min} ↓ 52%	Co-administration should be avoided.
	Posaconazole	Concentrations of posaconazole and telaprevir may be ↑	Use with caution and monitor for posaconazole-associated toxicities, including QT prolongation. Consider monitoring posaconazole concentration and adjust dose accordingly.
	Rifabutin	Concentrations of telaprevir may be ↑, while rifabutin concentrations may be ↑	Co-administration should be avoided
	Rifampin	Telaprevir AUC ↓ 92%	Co-administration should be avoided
	Tenofovir	Tenofovir C_{max}, AUC, and C_{min} ↑ 30%–41%	Monitor for tenofovir-associated toxicities.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 13 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Telaprevir, continued	Voriconazole	Potential interaction; magnitude and direction unknown.	Co-administration should be avoided unless benefit is considered to outweigh risks; monitor for voriconazole-associated toxicities, including QT prolongation. Consider monitoring voriconazole concentration and adjust dose accordingly.
Tenofovir	Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir	Potential for competitive active tubular secretion with these antiviral drugs.	Monitor for efficacy and toxicities of the antiviral agents and tenofovir.
	Atazanavir	Atazanavir AUC ↓ 25%, C_{min} ↓ 40%; tenofovir AUC ↑ 24%.	Atazanavir dose should be 300 mg daily given with ritonavir 100 mg daily when co-administered with tenofovir; monitor for tenofovir-associated toxicities.
	Darunavir/ritonavir	Tenofovir AUC ↑ 22%, C_{min} ↑ 37%	Monitor for tenofovir-associated toxicities.
	Didanosine	Didanosine AUC and C_{max} ↑ 48%–60%	Co-administration should be avoided. If co-administered, didanosine dose should be decreased to 250 mg once daily.
	Lopinavir/ritonavir	Tenofovir AUC ↑ 34%	Monitor for tenofovir-associated toxicities.
	Telaprevir	Tenofovir C_{max}, AUC and C_{min} ↑ 30–41%	Monitor for tenofovir-associated toxicities.
Voriconazole	Boceprevir	Concentrations of voriconazole may be ↑	Use with caution. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Efavirenz	Voriconazole C_{max} ↓ 36–61%, AUC ↓ 55–77%; efavirenz C_{max} ↑ 38%, AUC ↑ 44%	Increase voriconazole maintenance dose to 400 mg q12h and decrease efavirenz to 300 mg daily. Consider monitoring voriconazole and/or efavirenz concentration and adjust doses accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Voriconazole, elvitegravir, and cobicistat concentrations may be ↑	Monitor for voriconazole-associated toxicities. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Etravirine	Voriconazole AUC ↑ 14%, C_{min} ↑ 23%; etravirine AUC ↑ 36%, C_{min} ↑ 52%	No dose adjustment necessary; monitor for etravirine-associated toxicities. Consider monitoring voriconazole concentration and adjust dose accordingly.

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 14 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Voriconazole, continued	Nevirapine	Potential for ↓ voriconazole concentrations; however, no formal interaction data are available.	Monitor for therapeutic efficacy of voriconazole; consider monitoring voriconazole concentrations and adjust dose accordingly.
	PI boosted with ritonavir	Voriconazole AUC ↓ 39% (studied with ritonavir 100 mg BID). No interaction data for individual boosted PIs; however, potential for ↑ PI concentrations and ↓ voriconazole concentrations.	Consider monitoring voriconazole concentrations and adjust dose accordingly; monitor for PI-associated toxicities.
	Rifabutin	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 3-fold.	Co-administration should be avoided, if possible; if used in combination, monitor voriconazole and rifabutin concentrations, clinical responses, and toxicities from both drugs.
	Rifampin	Voriconazole AUC ↓ 96%	Co-administration should be avoided.
	Rilpivirine	No PK data. Possible ↑ rilpivirine concentration	Monitor efficacies and toxicities of both drugs. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Telaprevir	Potential interaction; magnitude and direction unknown.	Co-administration should be avoided unless benefit is considered to outweigh risks; monitor for voriconazole-associated toxicities, including QT prolongation. Consider monitoring voriconazole concentration and adjust dose accordingly.

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily = C_{max} = maximum concentration; C_{min} = minimum concentration; CrCl = creatinine clearance; CYP3A4 = Cytochrome P450 3A4; ddA-TP = dideoxyadenosine triphosphate; DHA = dihydroartemisinin; PI = protease inhibitor; PK = pharmacokinetic; TID = three times a day

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Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 1 of 5) (Last updated May 7, 2013; last reviewed May 7, 2013)

Drugs	Common or Serious Adverse Reactions
Acyclovir	Generally well-tolerated. Crystalluria (with high dose or pre-existing renal impairment), neurotoxicity (high doses, especially in patients with renal impairment; 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	Generally well-tolerated. Nephrotoxicity with underlying renal insufficiency, nausea, asthenia
Albendazole	Nausea, vomiting, hepatotoxicity, hypersensitivity reaction, dizziness, headache, reversible alopecia Rarely: granulocytopenia, agranulocytosis, or 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/Clavulate 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, dyspnea; 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, headache, hemolytic anemia (rare), QTc prolongation
Artesunate	Generally well-tolerated. Bradycardia, dizziness, nausea and vomiting, skin rash, pruritus
Atovaquone	Rash, nausea, vomiting, diarrhea, hepatotoxicity, headache, hyperglycemia, fever
Atovaquone/Proguanil	Pruritus, rash, nausea, vomiting, abdominal pain, diarrhea, anorexia, EM, asthenia, dizziness, headache, oral ulcers, hepatotoxicity
Azithromycin	Nausea, vomiting, diarrhea, hepatotoxicity, ototoxicity (with prolonged use), rash, urticaria, pruritus, abdominal pain; risk of torsades de pointes, use with caution in patients with underlying QTc prolongation
Aztreonam	Diarrhea, hypersensitivity reaction (rare), thrombophlebitis
Benznidazole	Photosensitivity, allergic dermatitis, paresthesia, peripheral neuropathy, nausea, vomiting, abdominal pain, anorexia, weight loss
Boceprevir	Anemia, neutropenia, dysgeusia, dry mouth, nausea, headache, acute hypersensitivity reaction (urticarial, angioedema; rare)
Capreomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), neuromuscular blockade (associated with rapid infusion of large aminoglycoside doses), 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
Ceftriaxone	Generally well-tolerated. Cholelithiasis, rash, diarrhea, drug fever, *C. difficile*-associated diarrhea and colitis; IM injections: injection-site reactions, pain

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Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 2 of 5)

Drugs	Common or Serious Adverse Reactions
Cephalosporins	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 dose used in patients with renal insufficiency or elderly patients without dosage adjustment)
Chloroquine and Hydroxychloroquine	Headache, pruritus, skin pigmentation, nausea, vomiting, abdominal pain, diarrhea, anorexia, photosensitivity, visual disturbances, QTc prolongation, neuromyopathy (rarely with long-term use); hemolysis (with G6PD deficiency); hypersensitivity reaction (including TEN, SJS, and EM)
Cidofovir	Nephrotoxicity, proteinuria, ocular hypotony, anterior uveitis/iritis, neutropenia, metabolic acidosis, asthenia. 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 age >60 and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or in patients with renal dysfunction), seizures (rare)
Clarithromycin	Hepatotoxicity, ototoxicity (with high doses or prolonged use), headache, nausea, vomiting, abdominal cramps, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, QTc prolongation
Clindamycin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, arrhythmia associated with rapid IV infusion
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
Dapsone	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), neutropenia, rash, sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, hemolysis), peripheral neuropathy, hepatotoxicity
Doxycycline	Photosensitivity reaction, nausea, vomiting, diarrhea, esophageal ulceration, thrombophlebitis (with IV infusion)
Emtricitabine	Generally well-tolerated. Headache, nausea, hyperpigmentation, diarrhea, rash
Entecavir	Generally well-tolerated. Headache, fatigue, dizziness, nausea
Erythromycin	Nausea, vomiting, abdominal pain, hepatotoxicity, cholestatic jaundice, ototoxicity (hearing loss, tinnitus), rash, QTc prolongation and cardiac arrhythmia
Ethambutol	Optic neuritis (dose dependent), peripheral neuropathy, headache, nausea, vomiting, anorexia, hepatotoxicity, hyperuricemia, hypersensitivity reaction
Ethionamide	Gastrointestinal side effects (dose related): nausea, vomiting, diarrhea, abdominal pain, metallic taste, anorexia; dizziness, drowsiness, depression, hepatotoxicity, hypothyroidism (with or without goiter), gynecomastia
Famciclovir	Generally well-tolerated. Headache, nausea, vomiting, diarrhea
Flucytosine	Concentration-dependent bone marrow suppression (anemia, neutropenia, thrombocytopenia), diarrhea, nausea, vomiting, rash

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Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 3 of 5)

Drugs	Common or Serious Adverse Reactions
Fluconazole	Hepatotoxicity, rash, nausea, vomiting, diarrhea, abdominal discomfort, reversible alopecia (with doses ≥400 mg/d for >2 months)
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, confusion
Imipenem/Cilastatin	Hypersensitivity reaction (immediate or delayed); CNS effects—seizure, myoclonus, confusion (more frequent with impenem than meropenem and dorepenem [especially with higher doses, in patients with underlying CNS disorders, or with renal insufficiency]), nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, headache, bone marrow suppression, drug fever
Interferon-Alfa and Peginterferon-Alfa	Influenza-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)
Itraconazole	Hepatotoxicity, congestive heart failure, edema, hypokalemia, nausea, vomiting, diarrhea, abdominal pain, rash
Lamivudine	Generally well-tolerated. Nausea, vomiting
Levofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or in patients with renal dysfunction), seizures (rare)
Linezolid	Anemia, neutropenia, thrombocytopenia (especially with >2- to 4-week treatment), peripheral neuropathy, optic neuritis with long-term (months) 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)
Mefloquine	Depression, psychosis, rash (reports of TEN and SJS), nausea, vomiting, diarrhea, epigastric pain, agitation, dizziness, headache, insomnia, abnormal dreams, QTc prolongation, arrhythmias (extrasystole, sinus bradycardia)
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 it is rare if infused over 1 hour; anaphylaxis and anaphylactoid reaction; hepatotoxicity, thrombophlebitis, nausea, vomiting, diarrhea, hypokalemia, hemolysis (rare)

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Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 4 of 5)

Drugs	Common or Serious Adverse Reactions
Miconazole Buccal Tablets	Dysgeusia, diarrhea, nausea, vomiting, upper abdominal pain, headache, local reactions (oral discomfort, burning, pain, tongue/mouth ulceration, gingival pruritus, pain and swelling, dry mouth), hypersensitivity reaction (rare—may occur in patients with known hypersensitivity reaction to milk product concentrate)
Miltefosine	Nausea, vomiting, diarrhea, leukocytosis, thrombocytosis, nephrotoxicity, retinal degeneration
Moxifloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or in patients with renal dysfunction), seizures (rare)
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 & Procaine Penicillin G: IM injection-site reactions (pain and erythema) Aqueous Crystalline Penicillin G (IV): Thrombophlebitis, neurotoxicity at high doses (especially in patients with renal dysfunction)
Pentamidine	IV Infusion: Nephrotoxicity, infusion-related hypotension, thrombophlebitis, arrhythmias (including torsades de pointes), pancreatitis, hypoglycemia, hyperglycemia, diabetes mellitus, hepatotoxicity, electrolyte abnormalities, leukopenia, 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
Piperacillin-Tazobactam	Generally well-tolerated. Hypersensitivity reaction, rash, diarrhea, nausea, vomiting, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, thrombocytopenia (rare), impaired platelet aggregation, seizure (high dose in patients with renal insufficiency)
Primaquine	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), leukopenia, neutropenia, abdominal cramps, nausea, vomiting
Pyrazinamide	Hepatotoxicity, hyperuricemia, arthralgia, nausea, vomiting
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
Quinine	Headache, nausea, vomiting, diarrhea, cinchonism (tinnitus, vertigo, blurred vision), hypersensitivity reaction

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Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 5 of 5)

Drugs	Common or Serious Adverse Reactions
Ribavirin	Hemolytic anemia, dyspnea, hyperbilirubinemia, nausea, vomiting, anorexia, dyspepsia, rash, dry cough
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
Streptomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), pain upon IM injection
Sulfadiazine	Rash (including SJS, EM, TEN), anemia, neutropenia, thrombocytopenia, crystalluria with or without urolithiasis, renal insufficiency, nausea, vomiting, drug fever, hepatotoxicity
Telaprevir	Anemia, rash, pruritus, nausea, vomiting, dysgeusia, diarrhea, ano-rectal discomfort (hemorrhoid, pruritus), proctitis, severe cutaneous eruption (including SJS, EM, TEN)
Telbivudine	Generally well-tolerated. Nausea, vomiting, abdominal pain, increase in creatine kinase, headache, dizziness
Tenofovir	Renal insufficiency, proximal renal tubulopathy (with hypophosphatemia, hypouricemia, normoglycemic glycosuria), decrease in bone mineral density, nausea
Tetracycline	Photosensitivity, tooth discoloration if taken by infants and children, pruritus, esophageal ulceration, nausea, vomiting, diarrhea, hepatotoxicity, rash
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 (high doses, especially in patients with renal impairment; agitation, confusion, hallucination, seizure, coma)
Valganciclovir	Neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, confusion
Vancomycin	Infusion-related reaction (infusion-rate related, flushing, hypotension, rash), thrombophlebitis, rash, neutropenia, thrombocytopenia (rare), ototoxicity (associated with excessive concentration), nephrotoxicity (associated with high daily dose and high trough concentrations)
Voriconazole	Visual disturbances (with initial dosing), optic neuritis (with >28 days treatment), skin photosensitivity, rash, hepatotoxicity, peripheral edema, headache, delirium, hallucination, encephalopathy (associated with trough >5.5 mcg/mL), QTc prolongation, peripheral neuropathy (rare)

Key to Acronyms: CNS = central nervous system; 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

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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

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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.

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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.		

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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	

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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)

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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)

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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: $\frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{Serum Creatinine}}$

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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.

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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

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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.

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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

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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

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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

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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.

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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.

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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

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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.

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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

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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

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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.

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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.

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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

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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.

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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.

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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

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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

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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

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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

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RPT	rifapentine
SMX	sulfamethoxazole
TCA	trichloroacetic acid
TDF	tenofovir disoproxil fumarate
TMP	trimethoprim
TMP-SMX	trimethoprim-sulfamethoxazole
TVR	telaprevir
ZDV	zidovudine

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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

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Pneumocystis Pneumonia (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
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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.

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Toxoplasma gondii Encephalitis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
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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

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Member		Financial Disclosure	
		Company	Relationship
Montoya, Jose	*Stanford University*	None	N/A
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		• 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

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Cryptosporidiosis and Microsporidiosis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
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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

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Mycobacterium tuberculosis Infection and Disease (Last Reviewed: September 1, 2014; Last Updated:September 1, 2014)

Member		Financial Disclosure	
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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

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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.

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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.

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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.

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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.

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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 September 1, 2012, through September 1, 2014.

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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.

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Invasive Mycoses (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Ampel, Neil*	*University of Arizona*	None	N/A
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	• New England Research Institutes	• Adjudication Panel for Resolving Infection in Neutropenia with Granulocytes Study
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*	• Astellas	• Advisory Board, Consultant, Honoraria, Research Support
		• F2G	• Consultant
		• Merck	• Advisory Board, Consultant, Honoraria, Research Support
		• Pfizer	• Consultant, Honoraria, Research Support
		• Scynexis	• Consultant
		• Viamet	• 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.

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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.

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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.

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Human Papillomavirus Disease (Last Reviewed: February 1, 2016; Last Updated: February 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.

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Human Papillomavirus Disease (Last Reviewed: February 1, 2016; Last Updated: February 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.

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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.

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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.

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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.

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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.

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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.

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Pharmacology (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Dooley, Kelly	*Johns Hopkins University School of Medicine*	• Viiv Healthcare	• Research Support
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	*Johns Hopkins University*	• Barclay	• Consultant
		• Janssen	• Consultant
		• Maryland MADAP	• 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.

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Pregnancy (Last Reviewed: February 1, 2016; Last Updated: February 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.

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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.

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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.

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