Complete Summary

GUIDELINE TITLE

Treating opportunistic infections among HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 17;53(RR-15):1-118. [693 references]

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- July 08, 2008, Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin): A BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.
- January 24, 2008, Leukine (sargramostim): Voluntary market suspension of the current liquid formulation of sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting). The lyophilized form of the drug is not affected. See the U.S. Food and Drug Administration (FDA) web site for more information.

- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.
- September 11, 2007, Rocephin (ceftriaxone sodium): Roche informed healthcare professionals about revisions made to the prescribing information for Rocephin to clarify the potential risk associated with concomitant use of Rocephin with calcium or calcium-containing solutions or products.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Opportunistic infection among human immunodeficiency virus (HIV)-infected adults and adolescents, including:

- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- *Toxoplasma gondii* encephalitis
- Cryptosporidiosis
- Microsporidiosis
- *Mycobacterium tuberculosis* (TB) disease
- *Mycobacterium avium* complex (MAC) disease
- Bacterial respiratory disease
- Bacterial enteric disease
- Bartonellosis
- Syphilis
- Mucocutaneous candidiasis
- Cryptococcosis
- Histoplasmosis
- Coccidioidomycosis
- Aspergillosis
- Cytomegalovirus (CMV) disease
- Herpes simplex virus (HSV) disease
- Varicella zoster virus (VZV) disease

- Human herpesvirus-8 (HHV-8) disease
- Progressive multifocal leukoencephalopathy caused by JC virus
- Human papillomavirus (HPV) disease
- Hepatitis C virus (HCV) disease
- Hepatitis B virus (HBV) disease
- Geographic opportunistic infections of special consideration, including penicilliosis, leishmaniasis, paracoccidioidomycosis, isosporiasis, and Chagas disease

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To present disease-specific recommendations for the treatment of human immunodeficiency (HIV)-associated opportunistic infections among adults and adolescents in the United States and Western Europe
- To serve as a companion to *The United States Public Health Service/Infectious Diseases Society of America (IDSA) Guidelines for the Prevention of Opportunistic Infections in Persons Infected with the Human Immunodeficiency Virus* and *The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, as well as the Centers for Disease Control and Prevention guideline, *Treating Opportunistic Infections Among HIV-Exposed and Infected Children*

TARGET POPULATION

Human immunodeficiency virus (HIV)-infected adults and adolescents, including pregnant women, with opportunistic infections living in the United States and Western Europe

INTERVENTIONS AND PRACTICES CONSIDERED

1. Disease-specific Pharmocologic therapy (refer to the "Major Recommendations" field for specific medications and therapeutic regimens)
2. Nonpharmacologic interventions as appropriate (refer to the "Major Recommendations" field for specific indications), including:
    - Directly observed therapy (DOT) for patients with tuberculosis
    - Penicillin desensitization
    - Cryotherapy with liquid nitrogen
    - Trichloroacetic or bichloroacetic acid cauterization
    - Surgical excision of lesions (including laser surgery)
    - Loop electrosurgical excision procedure (LEEP)
    - Cone biopsy
    - Cerebral spinal fluid (CSF) examination
    - Lumbar puncture or CSF shunting
    - Vaccination with 23-valent polysaccharide pneumococcal vaccine, influenza vaccine, and hepatitis A vaccine
3. Treatment of symptoms
4. Supportive care, including hydration, nutritional support, counseling
5. Monitoring for recurrence, adverse reactions, and drug toxicities
6. Special considerations for pregnant women (e.g., Cesarean delivery)
7. Referral to specialists

MAJOR OUTCOMES CONSIDERED

- CD4+ cell count
- Mortality
- Signs and symptoms
- Recurrence of infection
- Fetal risk, including transmission of infection to fetus, morbidity, and mortality
- Toxicities, drug interactions, and the potential to induce drug resistance

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Supporting the Recommendation

I: Evidence from at least one properly designed randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of the Recommendation

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered**.
B. Moderate evidence for efficacy – or strong evidence for efficacy but only limited clinical benefit – support recommendation for use. **Should generally be offered**.
C. Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. **Optional**.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered**.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered**.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines were reviewed by respective members of each panel to ensure the recommendations were complete and in agreement, where possible, and appropriate.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the Centers for Disease Control and Prevention (CDC) and the National Guideline Clearinghouse (NGC): On September 19, 2008 the CDC released updated guidelines on hepatitis B. For more information see the NGC summary Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection.

Levels of evidence (I-III) and grades of recommendation (A-E) are defined at the end of the "Major Recommendations" field.

Refer to the original guideline document for information on epidemiology, clinical manifestations, and diagnosis for each opportunistic infection discussed.

Refer to Table 6 in the original guideline document for a summary of recommendations for treatment of acquired immune deficiency syndrome (AIDS)-associated opportunistic infections among adults; to Table 7 for information on common toxicities of systematic agents for treatment of opportunistic infections; Table 8 for information on drug interactions of clinical significance; and Table 9 for information on antiretroviral anti-infective drug combinations that should be avoided.

When to Initiate Antiretroviral Therapy (ART) in the Setting of an Opportunistic Infection (OI)

No consensus has been reached about the optimal time to start ART in the presence of a recently diagnosed OI. The decision to start potent ART should take into consideration the availability of effective therapy for the OI, the risk for drug interactions, overlapping drug toxicities, the risk for and consequences of the development of an inflammatory immune reconstitution syndrome, and the willingness and ability of patients to take and adhere to their regimens.

In cases of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), and Kaposi sarcoma, the early benefits of potent ART

outweigh any increased risk, and potent ART should be started as soon as possible (**AIII**). In the setting of tuberculosis (TB) disease, *Mycobacterium avium* complex (MAC), *Pneumocystis jiroveci* pneumonia (PCP), and cryptococcal meningitis, awaiting a response to OI therapy is usually warranted before initiating ART (**CIII**). When an OI occurs within 12 weeks of starting ART, treatment for the OI should be started, and ART should be continued (**AIII**). When an OI occurs despite complete virologic suppression (i.e., late OI), therapy for the OI should be initiated, potent ART should be continued, and if the $CD4^+$ T cell response to ART has been suboptimal, modification of the ART regimen may be considered (**CIII**). When an OI occurs in the setting of virologic failure, OI therapy should be started, antiretroviral resistance testing should be performed, and the ART regimen should be modified if possible to achieve better virologic control (**AI**).

Special Considerations During Pregnancy

For pregnant women who have had an OI diagnosed and are not on ART, immediate initiation of ART with OI therapy should be encouraged (**AIII**). Decisions about immediate versus delayed initiation of ART in pregnancy should take into account gestational age, maternal human immunodeficiency virus (HIV)-1 ribonucleic acid (RNA) levels and clinical condition, and potential toxicities and interactions between ART and OI drugs.

For additional information about special considerations of treating OI in pregnant women, please see the original guideline document as well as disease-specific recommendations below.

Pneumocystis jiroveci **Pneumonia (PCP)**

Treatment Recommendations

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice (**AI**). 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 of questionable efficacy and some evidence for a higher failure rate (**DII**). Oral outpatient therapy of TMP-SMX is highly effective among patients with mild-to-moderate disease (**AI**).

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

Patients with documented 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 corticosteroids as early as possible, and certainly within 72 hours after starting specific PCP therapy (**AI**). If steroids are started at a later time, their benefits are unclear, although the majority of clinicians would use them in such circumstances for patients with severe disease (**BIII**). The preferred corticosteroid dose and regimen is prednisone 40 mg by mouth twice a day for days 1 to 5, 40 mg daily for days 6 to 10, and 20 mg daily for days 11 to 21 (**AI**).

Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens include 1) dapsone and TMP for mild-to-moderate disease (**BI**) (this regimen may have similar efficacy and fewer side effects than TMP-SMX but is less convenient because of the number of pills); 2) primaquine plus clindamycin (**BI**) (this regimen is also effective in mild-to-moderate disease, and the clindamycin component can be administered intravenously for more severe cases; however, primaquine is only available orally); 3) intravenous pentamidine (**AI**) (generally the drug of second choice for severe disease); 4) atovaquone suspension (**BI**) (this is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects); and 5) trimetrexate with leucovorin (**BI**) (this is less effective than TMP-SMX but can be used if the latter is not tolerated and an intravenous regimen is needed). Leucovorin must be continued 3 days after the last trimetrexate dose. The addition of dapsone, sulfamethoxazole, or sulfadiazine to trimetrexate might improve efficacy on the basis of the sequential enzyme blockade of folate metabolism, although no study data exist to confirm this (**CIII**). Aerosolized pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse (**DI**).

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

Although the overall prognosis of patients whose degree of hypoxemia requires intensive care unit (ICU) admission or mechanical ventilation remains poor, survival in up to 40% of patients requiring ventilatory support has been reported in recent years. Because long-term survival is possible for patients in whom ART is effective, certain patients with AIDS and severe PCP should be offered ICU admission or mechanical ventilation when appropriate (e.g., when they have reasonable functional status) (**AII**).

Because of the potential for additive or synergistic toxicities associated with anti-PCP and antiretroviral therapies, certain health-care providers delay initiation of ART until after the completion of anti-PCP therapy, despite some suggestion of potential benefit for early ART (**CIII**). An immune recovery inflammatory syndrome has been described for PCP and might complicate the concurrent administration of anti-PCP treatment and ART.

Monitoring and Adverse Events

Careful monitoring during 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 promptly and maintained until the $CD4^+$ T lymphocyte count is >200 cells/microliter. If PCP occurred at a $CD4^+$ T lymphocyte count >200 cells/microliter, maintaining PCP prophylaxis for life regardless of the $CD4^+$ T cell response might be prudent; however, data about the most appropriate approach in this setting are limited.

Adverse reaction rates among patients with AIDS are high for TMP-SMX (20 to 85%). Common adverse effects are rash (30 to 55%) (including Stevens-Johnson syndrome), fever (30 to 40%), leukopenia (30 to 40%), thrombocytopenia (15%), azotemia (1 to 5%), hepatitis (20%), and hyperkalemia. Supportive care for common adverse effects should be attempted before discontinuing TMP-SMX (**AIII**). Rashes can often 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 G-6-PD deficiency), rash, and fever with dapsone; azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, fever, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine; anemia, rash, fever, diarrhea, and methemoglobinemia with primaquine and clindamycin; headache, nausea, diarrhea, rash, fever, and transaminase elevations with atovaquone; and bone marrow suppression, fever, rash, and hepatitis with trimetrexate.

Management of Treatment Failure

Clinical failure is defined by the lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Treatment failure attributed to treatment-limiting toxicities occurs in up to one third of patients. Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease. Adding or switching to another regimen is the appropriate management for treatment-related toxicity (**BII**). No convincing clinical trials exist to base recommendations for the management of treatment failure attributed to lack of drug efficacy. It is important to 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 for such deterioration. Bronchoscopy with bronchoalveolar lavage should be strongly considered even if it was conducted before initiating therapy.

If TMP-SMX has failed or must be avoided for toxicity in moderate-to-severe disease, the common practice is to use parenteral pentamidine, primaquine combined with clindamycin, or trimetrexate (with or without oral dapsone) plus leucovorin (**BII**). For mild disease, atovaquone is a reasonable alternative (**BII**). Although one meta-analysis concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy, no prospective clinical trials have evaluated the optimal approach to patients who fail therapy with TMP-SMX.

Prevention of Recurrence

Patients who have a history of PCP should be administered secondary prophylaxis (chronic maintenance therapy) for life with TMP-SMX unless immune reconstitution occurs as a result of ART (**AI**). For patients who are intolerant of TMP-SMX, alternatives are dapsone, dapsone combined with pyrimethamine, atovaquone, or aerosolized pentamidine.

Secondary prophylaxis should be discontinued for adult and adolescent patients whose $CD4^+$ T lymphocyte cell count has increased from <200 cells/microliter to >200 cells/microliter for at least 3 months as a result of ART (**AI**). Secondary prophylaxis should be reintroduced if the $CD4^+$ T lymphocyte count decreases to <200 cells/microliter (**AIII**) or if PCP recurs at a $CD4^+$ T lymphocyte count of >200 cells/microliter (**CIII**).

Special Considerations During Pregnancy

Diagnostic considerations during pregnancy are the same as for nonpregnant women. Indications for therapy are the same as for nonpregnant women. 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**). Neonatal care providers should be informed of maternal sulfa or dapsone therapy if used near delivery because of the theoretical increased risk for hyperbilirubinemia and kernicterus.

Pentamidine is embryotoxic but not teratogenic among rats and rabbits. Trimetrexate should not be used because of teratogenicity at low doses in multiple animal studies, fetopathy in humans associated with use of the biochemically similar agents methotrexate and aminopterin, and the potential negative effects on placental and fetal growth (**EIII**). Adjunctive corticosteroid therapy should be used as indicated in nonpregnant adults (**AIII**). Maternal fasting and postprandial glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk for glucose intolerance is increased.

Rates of preterm labor and preterm delivery are increased with pneumonia during pregnancy. Pregnant women with pneumonia after 20 weeks of gestation should be monitored for evidence of contractions (**BII**).

Toxoplasma gondii **Encephalitis**

Treatment Recommendations

The initial therapy of choice consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin (**AI**). Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation. Use of leucovorin prevents the hematologic toxicities associated with pyrimethamine therapy. The preferred alternative regimen for patients unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin (**AI**).

TMP-SMX was reported in a small (77 patient) randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with this regimen, pyrimethamine plus sulfadiazine with leucovorin is the preferred therapy (**BI**). For patients who cannot take an oral regimen, no well-studied options exist. No parenteral formulation of pyrimethamine exists; the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Therefore, certain specialists will treat severely ill patients requiring parenteral therapy initially with oral pyrimethamine plus parenteral TMP-SMX or parenteral clindamycin (**CIII**).

At least three regimens have activity in the treatment of toxoplasmic encephalitis (TE) in at least two, nonrandomized, uncontrolled trials, although their relative efficacy compared with the previous regimens is unknown: 1) atovaquone (with meals or oral nutritional supplements) plus pyrimethamine plus leucovorin (**BII**); 2) atovaquone combined with sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent (**BII**) (if atovaquone is used alone, measuring plasma levels might be helpful given the high variability of absorption of the drug among different patients; plasma levels of $\geq$18.5 micrograms/mL are associated with an improved response rate); and 3) azithromycin plus pyrimethamine plus leucovorin daily (**BII**).

The following regimens have been reported to have activity in the treatment of TE in small cohorts of patients or in case reports of one or a few patients: clarithromycin plus pyrimethamine (**CIII**); 5-fluoro-uracil plus clindamycin (**CIII**), dapsone plus pyrimethamine plus leucovorin (**CIII**); and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin (**CIII**). Although the clarithromycin dose used in the only published study was 1 g twice a day, doses >500 mg have been associated with increased mortality in HIV-1-infected patients treated for disseminated MAC. Doses >500 mg twice a day should not be used (**DIII**).

Acute therapy should be continued for at least 6 weeks, if there is clinical and radiologic improvement (**BII**). Longer courses might be appropriate if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. Adjunctive corticosteroids (e.g., dexamethasone) should be administered when clinically indicated only for treatment of a mass effect associated with focal lesions or associated edema (**BIII**). Because of the potential immunosuppressive effects of corticosteroids, they should be discontinued as soon as clinically feasible. Patients receiving corticosteroids should be closely monitored for the development of other OIs, including cytomegalovirus retinitis and TB disease.

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

Monitoring and Adverse Events

Changes in antibody titers are not useful for monitoring responses to therapy. Patients should be routinely monitored for adverse events and clinical and radiologic improvement (**AIII**). Common pyrimethamine toxicities include rash, nausea, and bone-marrow suppression (neutropenia, anemia, and thrombocytopenia) that can often be reversed by increasing the dose of leucovorin to 50 to 100 mg/day administered in divided doses (**CIII**).

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Drug interactions between anticonvulsants and antiretroviral agents should be carefully evaluated and doses adjusted according to established guidelines.

Management of Treatment Failure

A brain biopsy, if not previously performed, should be strongly considered for patients who fail to respond to initial therapy (**BII**) as defined by clinical or radiologic deterioration during the first week despite adequate therapy or lack of clinical improvement within 2 weeks. For those who undergo brain biopsy and have confirmed histopathologic evidence of TE, a switch to an alternative regimen as previously described should be considered (**BIII**). Recurrence of disease during secondary maintenance therapy following an initial clinical and radiographic response is unusual if patients adhere to their regimen.

Prevention of Recurrence

Patients who have successfully completed a 6-week course of initial therapy for TE should be administered lifelong secondary prophylaxis (i.e., chronic maintenance therapy) unless immune reconstitution occurs because of ART (**AI**). Adult and adolescent patients appear to be at low risk for recurrence of TE when they have successfully completed initial therapy for TE, remain asymptomatic with respect to signs and symptoms of TE, and have a sustained (i.e., $\geq$6 months) increase in their $CD4^+$ T lymphocyte counts to >200 cells/microliter on ART. The numbers of such patients who have been evaluated remain limited. On the basis of these observations and inference from more extensive data about safety of discontinuing secondary prophylaxis for other OIs during advanced HIV-1 disease, discontinuing chronic maintenance therapy among such patients is a reasonable consideration (**CIII**). Certain health-care providers would obtain an MRI of the brain as part of their evaluation to determine whether discontinuation of therapy is appropriate and might be reluctant to stop therapy if any mass lesion or contrast enhancement persists (**CIII**). Secondary prophylaxis should be started again if the $CD4^+$ T lymphocyte count decreases to <200 cells/microliter (**AIII**).

Special Considerations During Pregnancy

Documentation of maternal *T. gondii* serologic status should be obtained during pregnancy. Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or suspected symptomatic disease in the mother. Pediatric care providers should be informed if the HIV-1-infected mother is seropositive for *T. gondii* infection to allow evaluation of the neonate for evidence of congenital infection. Pregnant HIV-1-infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine or other appropriate specialist (**BIII**).

Treatment should be the same as in nonpregnant adults (**BIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk for defects and, therefore, it can be administered to pregnant women. Pediatric providers should be notified if sulfadiazine is continued until delivery because its use might increase the risk for neonatal hyperbilirubinemia and kernicterus.

Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented occurrences of transmission with reactivation of chronic infection in HIV-1-infected women with severe immunosuppression. Because the risk for transmission with

chronic infection appears low, routine evaluation of the fetus for infection with amniocentesis or cordocentesis is not indicated. Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-1-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy.

Cryptosporidiosis

Treatment Recommendations

ART with immune restoration (an increase of $CD4^+$ T lymphocyte count to >100 cells/microliter) is associated with complete resolution of cryptosporidiosis, and all patients with cryptosporidiosis should be offered ART as part of the initial management of their infection (**AII**). No consistently effective pharmacologic or immunologic therapy directed specifically against *Cryptosporidium parvum* exists. Approximately 95 interventional agents have been tried for the treatment of cryptosporidiosis with no consistent success.

Paromomycin, a nonabsorbable aminoglycoside that is indicated for the treatment of intestinal amebiasis, is effective in high doses for the treatment of cryptosporidiosis in animal models. A meta-analysis of 11 published paromomycin studies in humans reported a response rate of 67%. However, relapse was common in certain studies, with long-term success rates of only 33%. Two randomized controlled trials have compared paromomycin with placebo among patients with AIDS and cryptosporidiosis; modest, but statistically significant improvement in symptoms and oocyst shedding was demonstrated in one, but no difference from placebo was observed in the other. A small open-label study suggested a substantial benefit of paromomycin when used in combination with azithromycin, but few cures were noted. Therefore, efficacy data do not support a recommendation for the use of paromomycin for therapy, although the drug appears to be safe (**CIII**).

Nitazoxanide, an orally administered nitrothiazole benzamide, has in vivo activity against a broad range of helminths, bacteria, and protozoa, including cryptosporidia. A short-term study among patients with HIV-1 infection documented increased cure rates compared with controls (based on clearance of organisms from stool and reduced rates of diarrhea) among patients with $CD4^+$ T lymphocyte counts >50 cells/microliter, but not in those with $CD4^+$ T lymphocyte counts <50 cells/microliter. Available data do not warrant a definite recommendation for use of this agent in this setting, but the drug has been approved by the U.S. Food and Drug Administration (FDA) for use in children and is expected to be approved for use in adults (**CIII**).

Treatment of persons with cryptosporidiosis should include symptomatic treatment of diarrhea (**AIII**). Rehydration and repletion of electrolyte losses by either the oral or intravenous route is important. Severe diarrhea, which might be >10 L/day among patients with AIDS, often requires intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions that contain glucose, sodium bicarbonate, potassium, magnesium, and phosphorus (**AIII**).

Treatment with antimotility agents can play an important adjunctive role in therapy, but these agents are not consistently effective (**BIII**). Loperamide or tincture of opium will often palliate symptoms. Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved for the treatment of secreting tumor induced diarrhea, is no more effective than other oral antidiarrheal agents, and is generally not recommended (**DII**).

Monitoring and Adverse Events

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition and should receive supportive treatment. Total parenteral nutrition might be indicated in certain patients (**CIII**).

Management of Treatment Failure

Supportive treatment and optimizing ART to achieve full virologic suppression are the only feasible approaches to the management of treatment failure (**CIII**).

Prevention of Recurrence

No drug regimens are proven to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

As with nonpregnant woman, initial treatment efforts should rely on rehydration and initiation of ART. Pregnancy should not preclude the use of ART.

Microsporidiosis

Treatment Recommendations

ART with immune restoration (an increase of $CD4^+$ T lymphocyte count to >100 cells/microliter) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *Enterocytozoon bieneusi*. All patients should be offered ART as part of the initial management of their infection (**AII**). Nevertheless, data indicate that microsporidia are suppressed but not eliminated.

No specific therapeutic agent is active against *E. bieneusi* infection. A controlled clinical trial suggests that *E. bieneusi* might respond to oral fumagillin (60 mg/day), a water insoluble antibiotic made by *Aspergillus fumigatus* (**BII**). However, fumagillin is not available for systemic use in the United States. One report indicates that 60 days of nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART. However, the effect might be minimal among patients with low $CD4^+$ T cell counts. Nitazoxanide is approved for use among children and is expected to be approved by the FDA for use among adults.

Albendazole and fumagillin have demonstrated consistent activity against other microsporidia in vitro and in vivo. Albendazole, a benzimidazole that binds to b-

tubulin, has activity against many species of microsporidia, but it is not effective for *Enterocytozoon* infections, although fumagillin has activity in vitro and in vivo.

Albendazole is recommended for initial therapy of intestinal and disseminated (not ocular) microsporidiosis caused by microsporidia other than *E. bieneusi* (**AII**). Itraconazole also might be useful in disseminated disease when combined with albendazole especially in infections caused by *Trachipleistophora* or *Brachiola* (**CIII**).

Ocular infections caused by microsporidia should be treated with topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 mg/mL of fumagillin) (**BII**). 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 the urine or in nasal smears. In such cases, the use of albendazole as a companion systemic agent is recommended (**BIII**).

Metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis (**DII**). Fluid support should be offered if diarrhea has resulted in dehydration (**AIII**). Malnutrition and wasting should be treated with nutritional supplementation (**AIII**).

Monitoring and Adverse Events

Albendazole side effects are rare but hypersensitivity (rash, pruritis, fever), neutropenia (reversible), central nervous system (CNS) effects (dizziness, headache), gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Albendazole is not 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.

Management of Treatment Failure

Supportive treatment and optimizing ART to attempt to achieve full virologic suppression are the only feasible approaches to the management of treatment failure (**CIII**).

Prevention of Recurrence

Treatment for ocular microsporidiosis should be continued indefinitely because recurrence or relapse might follow treatment discontinuation (**BIII**). Whether treatment can be safely discontinued after immune restoration with ART is unknown, although it is reasonable, on the basis of the experience with discontinuation of secondary prophylaxis (chronic maintenance therapy) for other opportunistic infections during advanced HIV-1 disease, to discontinue chronic maintenance therapy if patients remain asymptomatic with regard to signs and symptoms of microsporidiosis and have a sustained (e.g., $\geq$6 months) increase in their $CD4^+$ T lymphocyte counts to levels >200 cells/microliter after ART (**CIII**).

Special Considerations During Pregnancy

Among animals (i.e., rats and rabbits), albendazole is embryotoxic and teratogenic at dosages of 30 mg/kg body weight. Therefore, albendazole is not recommended for use among pregnant women (**DIII**). However, well-controlled studies in human pregnancy have not been performed. 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 among pregnant women (**EIII**). Topical fumagillin has not been associated with embryotoxic or teratogenic effects among pregnant women and might be considered when therapy with this agent is appropriate (**CIII**).

Mycobacterium tuberculosis **Disease**

Treatment Recommendations

Treatment of HIV-1-related TB disease should follow the general principles developed for TB treatment among non-HIV-infected persons (**AI**). Early diagnosis and treatment are critical. Because of the severity of TB disease among immunocompromised patients, directly observed therapy (DOT) is strongly recommended for patients with HIV-1-related TB (**AI**). Multiple drugs and DOT are used to provide effective therapy, to prevent acquired drug resistance during treatment, and to allow cure with a relatively short course of treatment (6 to 9 months).

HIV-1-infected patients have other social and medical needs and treatment success is enhanced by a case-management approach, which incorporates assistance with all of these needs (enhanced DOT) in addition to providing DOT.

Multiple concerns should be considered in the treatment of HIV-1-associated TB disease. First, treatment is effective, but the optimal duration of treatment is uncertain. Second, acquired drug resistance is unusual with the use of DOT, but does occur among HIV-1-infected persons. Third, the risk for acquired rifamycin resistance has led to specific recommendations about dosing frequency. Finally, the use of potent ART among patients being treated for TB is complicated by overlapping drug toxicity profiles, drug-drug interactions, and an increase in TB manifestations during immune reconstitution (paradoxical reactions). Recent studies indicate that, with careful attention to these complicating factors, the prognosis of HIV-1-associated TB disease can be substantially improved with the provision of potent ART (**AII**), although the optimal relative timing between anti-TB and HIV therapy is uncertain.

Treatment of drug susceptible TB disease in HIV-1-infected adults should include the use of a 6-month regimen consisting of an initial phase of isoniazid (INH), rifampin (RIF) or rifabutin, pyrazinamide (PZA), and ethambutol (EMB) given for 2 months followed by INH and RIF (or rifabutin) for 4 months when the disease is caused by organisms known or presumed to be susceptible to first-line anti-TB drugs (**AI**). When the organism is susceptible to INH, RIF, and PZA, EMB should be discontinued (**AI**).

The optimal duration of therapy for HIV-1-related TB disease remains controversial. Studies in developing countries have shown that patients with HIV-1-related TB respond well to standard 6-month treatment regimens, with rates of treatment failure and relapse similar to those of HIV-uninfected patients. However, it is unclear whether these results are applicable to patients with advanced HIV-1 disease and TB. While awaiting definitive randomized comparisons in HIV-1-infected patients with TB disease, 6 months of therapy is probably adequate for the majority of cases, but prolonged therapy (up to 9 months) is recommended (as in HIV-negative patients) for patients with a delayed clinical or bacteriological response to therapy (symptomatic or positive culture results at or after 2 months of therapy, respectively) or perhaps with cavitary disease on chest radiograph (**BII**).

Intermittent dosing (twice- or thrice- weekly) facilitates DOT by decreasing the total number of encounters required between the patient and the provider, making observed therapy more practical to deliver. However, once- or twice-weekly dosing has been associated with an increased rate of acquired rifamycin resistance among patients with advanced HIV-1 disease ($CD4^+$ T lymphocyte count <100 cells/microliter). Acquired rifamycin resistance was relatively common with once-weekly rifapentine plus INH and also occurred in trials of twice-weekly rifabutin plus INH and twice-weekly RIF plus INH. Therefore, once-weekly rifapentine is contraindicated among HIV-1-infected patients (**EI**), and it is recommended that RIF- and rifabutin-based regimens be given at least three times a week for patients with TB and advanced HIV-1 disease ($CD4^+$ T lymphocyte count <100 cells/microliter) (**AII**). Although treatment approaches to this population need to be further evaluated in prospective trials, a prudent management strategy consists of daily DOT during the first 2 months of therapy and thrice-weekly DOT during the continuation phase of anti-TB therapy (**BII**).

Monitoring and Adverse Events

Close follow-up, consisting of clinical, bacteriologic, and occasionally, laboratory and radiographic evaluations, is essential to ensure treatment success. In patients with pulmonary TB, at least one sputum specimen for microscopic examination and culture should be obtained at monthly intervals until two consecutive specimens are negative on culture (**AII**). Drug susceptibility tests should be repeated on isolates from patients who have positive cultures after 3 months of treatment. Patients who have positive cultures after 4 months of treatment should be considered as having failed therapy and managed accordingly. For patients with extrapulmonary TB, the frequency and types of evaluations will depend on the sites involved and the ease with which specimens can be obtained.

A detailed clinical assessment should be performed at least monthly to identify possible medication intolerance and to assess adherence. As a routine, monitoring blood tests for patients being treated with first-line drugs unless baseline abnormalities were identified is unnecessary (**AII**). More frequent clinical and laboratory monitoring is indicated for patients with underlying liver disease, including hepatitis C coinfection.

INH, RIF, and PZA all can cause drug-induced hepatitis, and the risk might be increased in patients taking other potentially hepatotoxic agents or in persons with underlying liver dysfunction. However, because of the effectiveness of these

drugs (particularly INH and RIF), they should be used, if at all possible, even in the presence of preexisting liver disease (**AIII**). Frequent clinical and laboratory monitoring should be performed to detect any exacerbation.

Independent of HIV status for all patients with TB disease, multiple treatment options exist if serum aminotransaminases are >3 times the upper limit of normal before the initiation of treatment, and the abnormalities are not thought to be caused by TB disease. One option is to use standard therapy with frequent monitoring. A second option is to treat with RIF, EMB, and PZA for 6 months, avoiding INH (**BII**). A third option is to treat with INH and RIF for 9 months, supplemented by EMB for the first 2 months, thereby avoiding PZA (**BII**). Among patients with severe liver disease, a regimen with only one hepatotoxic agent, generally RIF plus EMB, can be given for 12 months, preferably with another agent, such as a fluoroquinolone, for the first 2 months (**CIII**). As previously indicated, treatment might need to be lengthened for patients who are HIV-1-infected. For patients who develop worsening hepatic function on treatment, a specialist should be consulted.

Tests to monitor hepatotoxicity (aminotransferases, bilirubin, and alkaline phosphatase), renal function (serum creatinine), and platelet count should be obtained for all patients started on treatment for TB. At each monthly visit, patients taking EMB should be asked about possible visual disturbances including blurred vision or scotomata. Monthly testing of visual acuity and color discrimination is recommended for patients taking doses that, on a milligram per kilogram basis, are greater than those listed in recommended doses and for patients receiving the drug for >2 months.

Patients with TB disease caused by strains of *M. tuberculosis* resistant to at least INH and RIF (multidrug-resistant [MDR]) are at high risk for treatment failure and further acquired drug resistance. Such patients should be referred to or have consultation obtained from specialized treatment centers as identified by the local or state health departments or the Centers for Disease Control and Prevention (CDC). Although patients with strains resistant to RIF alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be managed in consultation with an expert.

Antiretroviral Therapy in the Management of TB Disease and Paradoxical Reactions

Rifamycin drugs are essential components of short-course regimens for treatment of TB disease. However, substantial adverse pharmacologic interactions occur between rifamycins and commonly used antiretroviral drugs (e.g., protease inhibitors [PIs] and non-nucleoside reverse transcriptase inhibitors [NNRTIs]) as a result of changes in drug metabolism resulting from induction of the hepatic cytochrome P-450 (CYP450) enzyme system. Of the available rifamycins, RIF is the most potent CYP450 inducer and rifabutin has substantially less inducing activity. Despite such interactions, a rifamycin should generally not be excluded from the TB treatment regimen among patients receiving potent ART, except in unusual circumstances (**AII**).

Either RIF or rifabutin can be used with NRTIs. Rifabutin can be used with certain PIs or NNRTIs (other than delavirdine) and has fewer problematic drug interactions than does rifampin (see Table 5, titled "Recommended dose adjustments when patients are administered rifabutin concurrently with antiretroviral drugs," in the original guideline document). Adjustments in rifabutin or elements of the ART regimen might be necessary with certain combinations. Two antiretroviral drug regimens have been associated with a favorable outcome when administered with RIF: efavirenz (potentially using an increased dose of 800 mg/day) plus 2 NRTIs and ritonavir (600 mg twice daily) plus 2 NRTIs. Serum concentrations of nevirapine might be adequate even in the presence of concentrations of RIF associated with enzyme induction, but clinical data are lacking. RIF should not be used with nelfinavir, saquinavir, indinavir, amprenavir, atazanavir, or dual PI combinations using low dose ritonavir ($\leq$200 mg twice daily) for which dosing guidelines are not available (**EII**).

The optimal time for initiating ART during TB treatment is unknown. Because of the risk for prolonged airborne transmission of *M. tuberculosis*, initiation of treatment for TB disease should never be delayed (**AI**). Early initiation of ART (within the first 2 to 4 weeks after the start of TB therapy) might decrease HIV-1 disease progression but might be associated with a relatively high incidence of side effects and paradoxical reactions (some severe enough to warrant discontinuation of both antiretroviral and anti-TB drugs). Delaying the initiation of ART for 4 to 8 weeks after starting antituberculous therapy has the potential advantages of being better able to ascribe a specific cause for a drug side effect, decreasing the severity of paradoxical reactions, and decreasing the adherence challenge for the patient. Until controlled studies are conducted to evaluate the optimal time for starting ART in patients with HIV-1-associated TB disease, this decision should be individualized on the basis of the patient's initial response to TB therapy, occurrence of side effects, and acceptance of multidrug ART. For these considerations, health-care providers should avoid beginning the simultaneous administration of both potent ART and combination chemotherapy for TB; most health-care providers would wait at least 4 to 8 weeks (**BIII**). Patients already receiving ART at the time treatment for TB is started require a careful assessment of the ART regimen and, if necessary, changes to ensure optimum treatment of the HIV-1 infection in the setting of TB therapy.

Because of the difficulties associated with the accurate diagnosis of an adverse drug reaction and in determining the responsible agent, the first-line anti-TB drugs should not be stopped permanently without strong evidence that the anti-TB drug was the cause of the reaction. In such situations, consultation with an expert in treating TB in persons with HIV-1 infection is recommended.

Patients might experience temporary exacerbation of symptoms, signs, or radiographic manifestations of TB disease after beginning anti-TB treatment. This phenomenon is termed a paradoxical (or immune reconstitution) reaction. This reaction occurs among non-HIV-1-infected persons, but it is more common among those with HIV-1 infection, particularly those treated with ART. These reactions presumably develop as a consequence of reconstitution of immune responsiveness brought about by ART or perhaps by treatment of TB itself. Signs of a paradoxical reaction can include high fevers, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrations, and increasing pleural

effusions. Such findings should be attributed to a paradoxical reaction only after a thorough evaluation has excluded other possible causes, especially TB therapy failure.

A paradoxical reaction that is not severe should be treated symptomatically with nonsteroidal anti-inflammatory agents without a change in anti-TB or antiretroviral therapy (**BIII**). Approaches to the management of severe reactions (e.g., high fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, and sepsis syndrome) have not been studied. However, case reports have documented improvements with the use of prednisone or methylprednisolone used at a dose of approximately 1 mg/kg body weight and gradually reduced after 1 to 2 weeks (**CIII**).

Management of Drug Resistance and Treatment Failure

If resistance to INH (with or without resistance to streptomycin) is detected, INH and streptomycin, if used, should be discontinued and the patient treated with a 6-month regimen of RIF, PZA, and EMB, which is nearly as effective as the conventional INH-containing regimen (**BII**). Alternatively, treatment with RIF and EMB for 12 months can be used, preferably with PZA during at least the initial 2 months (**BII**).

Treatment regimens for TB disease caused by RIF monoresistant strains are less effective, and patients infected with these strains are at increased risk for relapse and treatment failure. A minimum of 12 to 18 months of treatment with INH, EMB, and a fluoroquinolone (e.g., levofloxacin) with PZA administered during the first 2 months is recommended (**BIII**). An injectable agent (e.g., amikacin or capreomycin) might be included in the first 2-3 months for patients with severe disease.

Patients with MDR-TB are at high risk for treatment failure and relapse and require especially close follow-up during (and often after) treatment. Treatment regimens for MDR-TB should be individualized, taking into account the resistance pattern, relative activities of available anti-TB agents, the extent of disease, and presence of comorbid conditions. The management of MDR-TB is complex and should be undertaken only by an experienced specialist or in close consultation with specialized treatment centers (**AIII**).

Prevention of Recurrence

Secondary prophylaxis (chronic maintenance therapy) for patients who have successfully completed a recommended regimen of treatment for TB disease is unnecessary (**DII**). However, reinfection can occur.

Special Considerations During Pregnancy

HIV-1-infected pregnant women who do not have documentation of a negative tuberculin skin test (TST) result during the preceding year should be tested during pregnancy. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-1-infected pregnant women is not recommended.

The diagnostic evaluation for TB disease in pregnant women is the same as for nonpregnant adults. Chest radiographs with abdominal shielding result in minimal fetal radiation exposure. An increase in pregnancy complications, 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.

Therapy of TB disease during pregnancy should be the same as for the nonpregnant adult, but with attention given to the following considerations (**BIII**):

- INH is not teratogenic in animals or humans. Hepatotoxicity might occur more frequently in pregnancy and the postpartum period. Certain health-care providers recommend monthly monitoring of transaminases during pregnancy and the postpartum period (**CIII**).
- RIF is not teratogenic in humans. Because of a potential increased risk for RIF-related hemorrhagic disease among neonates born to women receiving anti-TB therapy during pregnancy, prophylactic vitamin K, 10 mg, should be administered to the neonate (**BIII**).
- PZA is not teratogenic among animals. Experience is limited with use in human pregnancy. Although World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of PZA 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. If PZA is not included in the initial treatment regimen, the minimum duration of therapy should be 9 months.
- EMB 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 EMB, but changes in visual acuity have not been detected in infants born after exposure in utero.

Experience during pregnancy with the majority of the second line drugs for TB is limited. MDR-TB in pregnancy should be managed in consultation with an expert. 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:

- Although no longer a first line agent, streptomycin use has been associated with a 10% rate of VIII nerve toxicity in infants exposed in utero; its use during pregnancy should be avoided if possible (**DIII**).
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy in utero; like streptomycin, this agent should generally be avoided if possible (**DIII**). There is a theoretical risk of ototoxicity in the fetus 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 with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy and among children aged <18 years (**CIII**). However, >200 cases

of ciprofloxacin use in pregnancy have been reported to various pregnancy registries, and its use has not been associated with arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for drug-resistant TB, if required based on susceptibility testing (**CIII**).

- Para-aminosalicylic acid (PAS) has been associated with occipital bone defects when administered during pregnancy to rats. PAS is not teratogenic among rats or rabbits. A possible increase in limb and ear anomalies was reported among 143 pregnancies with first trimester exposure in one study. No specific pattern of defects and no increase in rate of defects have been detected 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 following 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.
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

Disseminated *Mycobacterium avium* Complex (MAC) Disease

Treatment Recommendations

Initial treatment of MAC disease should consist of two antimycobacterial drugs to prevent or delay the emergence of resistance (**AI**). Clarithromycin is the preferred first agent (**AI**); it has been studied more extensively than azithromycin and appears to be associated with more rapid clearance of MAC from the blood. However, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin (**AII**). Ethambutol is the recommended second drug (**AI**). Some clinicians would add rifabutin as a third drug (**CI**). One randomized clinical trial demonstrated that the addition of rifabutin to the combination of clarithromycin and ethambutol for the treatment of disseminated MAC disease improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance. These studies were completed before the availability of effective ART. The addition of rifabutin should be considered in persons with advanced immunosuppression ($CD4^+$ T lymphocyte count <50 cells/microliter), 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 are most likely (**CIII**). If rifabutin cannot be used because of drug interactions or intolerance (see Table 5, titled "Recommended dose adjustments when patients are administered rifabutin concurrently with antiretroviral drugs," in the original guideline document), a third or fourth drug may be selected from among either the fluoroquinolones (ciprofloxacin or levofloxacin) or parenteral amikacin (see Table 6, titled "Treatment of AIDS-associated opportunistic infections among adults," in the original guideline document), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling (**CIII**).

Patients who have had disseminated MAC disease diagnosed and who have not previously been treated with or are not receiving potent ART should generally have ART initiated simultaneously or within 1 to 2 weeks of initiation of antimycobacterial therapy for MAC disease (**CIII**). If ART has already been instituted, it should be continued and optimized for patients with disseminated

MAC disease, unless drug interactions preclude the safe concomitant use of antiretroviral and antimycobacterial drugs (**CIII**).

Persons who have symptoms of moderate-to-severe intensity because of an immune recovery inflammatory syndrome in the setting of ART should receive treatment initially with nonsteroidal, anti-inflammatory agents (**CIII**). If symptoms fail to improve, short-term (4 to 8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily (QD), has been successful (**CIII**).

Monitoring and Adverse Events

Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2-4 weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response might be delayed. A repeat blood culture for MAC should be obtained 4-8 weeks after initiation of antimycobacterial therapy for patients who fail to have a clinical response to their initial treatment regimen (i.e., little or no reduction in fever or systemic symptoms).

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations of liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin >1 g per day for treatment of disseminated MAC disease have been associated with increased mortality and should not be used (**EI**). Rifabutin doses of ≥450 mg/day have been associated with higher risk for adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome p450 isoenzyme 3A4 and might be associated with a higher risk for experiencing uveitis or other adverse drug reactions.

Management of 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. Testing of MAC isolates for susceptibility to clarithromycin and azithromycin is recommended for patients who fail to microbiologically respond to initial therapy, relapse after an initial response, or develop MAC disease while receiving clarithromycin or azithromycin for prophylaxis; testing for susceptibility to clarithromycin, azithromycin, ethambutol, and rifabutin might be helpful in this setting, although the predictive value for ethambutol and rifabutin with regard to response to therapy has not been established. The majority of patients who failed clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected. Bactec® radiometric broth macrodilution is the recommended method for testing *M. avium* for susceptibility to antimicrobial agents. Minimum inhibitory concentrations (MICs) of ≥32 micrograms/mL for clarithromycin or ≥256 micrograms/mL for azithromycin are the suggested thresholds for determination of resistance based on the Bactec® method for radiometric susceptibility testing.

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 consisting of at least two new drugs not previously used and to which the isolate is susceptible from among the following: ethambutol, rifabutin,

ciprofloxacin or levofloxacin, or amikacin (**CIII**). Whether continuing clarithromycin or azithromycin in the face of resistance provides additional benefit is unknown (**CIII**). Clofazimine should not be used on the basis of the lack of efficacy demonstrated in randomized trials and the association with increased mortality (**EII**). Other second-line agents (e.g., ethionamide, thiacetazone [not available in the United States], or cycloserine) have been anecdotally combined with these drugs as salvage regimens. However, their role in this setting is not well defined. Among patients who have failed initial treatment for MAC disease or who have antimycobacterial drug resistant MAC disease, optimizing ART is an important adjunct to second-line or salvage therapy for MAC disease (**AIII**).

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for use (**DIII**). Interferon-gamma, tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor, and interleukin-12, either alone or in combination with other cytokines, appear to inhibit intracellular replication or enhance in vitro intracellular killing of *M. avium*. Use of these immunomodulators would be a logical adjuvant treatment for those who fail conventional antimycobacterial therapy.

Prevention of Recurrence

Adult and adolescent patients with disseminated MAC disease should receive lifelong secondary prophylaxis (chronic maintenance therapy) (**AII**), unless immune reconstitution occurs as a result of ART. Patients are at low risk for recurrence of MAC when they have completed a course of $\geq$12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g., $\geq$6 months) in their $CD4^+$ T lymphocyte counts to >100 cells/microliter after ART. Although the numbers of patients who have been evaluated remain limited and recurrences could occur, on the basis of these observations and on inference from more extensive data indicating the safety of discontinuing secondary prophylaxis for other opportunistic infections during advanced HIV-1 disease, discontinuing chronic maintenance therapy among such patients is reasonable (**BII**). Certain health-care providers recommend obtaining a blood culture for MAC, even for asymptomatic patients, before discontinuing therapy to substantiate that disease is no longer active, but it is not clear how often a positive culture will be obtained in such patients. Secondary prophylaxis should be reintroduced if the $CD4^+$ T lymphocyte count decreases to <100 cells/microliter (**AIII**).

Special Considerations During Pregnancy

Diagnostic considerations and indications for treatment are the same as among nonpregnant adults. Azithromycin is preferred over clarithromycin as the second agent with ethambutol or rifabutin because of the occurrence of birth defects in mice and rats associated with clarithromycin (**BIII**). Limited data among humans do not indicate an increased risk for defects among 122 women taking clarithromycin during the first trimester, although an increased rate of spontaneous abortions was noted. Limited data are available on the use of azithromycin during the first trimester in humans.

Bacterial Respiratory Disease

Treatment Recommendations

Therapy for HIV-1-related bacterial pneumonia should target the most commonly identified pathogens, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*. Treatment guidelines appropriate for HIV-1-uninfected patients are applicable to those with HIV-1 infection.

Specific recommended regimens include either an extended spectrum cephalosporin (e.g., cefotaxime or ceftriaxone) or a fluoroquinolone with activity against *S. pneumoniae* (e.g., levofloxacin, moxifloxacin, or gatifloxacin) (**AIII**). Combination therapy with a macrolide or quinolone plus a cephalosporin should be considered for those with severe illness (**AIII**).

For high-level penicillin-resistant isolates (MIC $\geq$4.0 micrograms/mL), therapy should be guided by susceptibility results. Determining whether meningitis is present is important because the recommended fluoroquinolones do not reliably attain adequate cerebrospinal fluid (CSF) levels for treating pneumococcal meningitis.

Among patients with severe immunodeficiency ($CD4^+$ T lymphocyte counts <100 cells/microliter), a known history of previous *Pseudomonas* infection, bronchiectasis, or relative or absolute neutropenia, broadening empiric coverage to include *P. aeruginosa* and other gram-negative bacilli should be considered. Possible options for therapy include ceftazidime, cefepime, piperacillin-tazobactam, a carbapenem, or high dose ciprofloxacin or levofloxacin. For ceftazidime and ciprofloxacin, other antimicrobial agents would be needed to provide optimal coverage for gram-positive infections.

Monitoring and Adverse Events

A clinical response (i.e., a reduction in fever and improvement in laboratory studies, physical findings, and respiratory symptoms) are generally observed 48 to 72 hours after initiation of appropriate therapy. Radiographic improvement might require additional time for demonstrable improvement.

Management of Treatment Failure

HIV-1-infected patients who fail to respond to appropriate antimicrobial therapy, as determined by a lack of reduction in fever, failure of the total white blood cell (WBC) to return toward normal, persistent or worsening pulmonary signs, symptoms or radiographic abnormalities, progressive hypoxemia or other evidence of progressive disease, should undergo further evaluation, especially bronchoalveolar lavage or transbronchial biopsy, to search for other infectious and noninfectious causes of pulmonary dysfunction. Broader spectrum antimicrobial therapy might be required while additional diagnostic testing is pursued. Management in consultation with an infectious disease specialist is recommended.

Prevention of Recurrence

The strategy most effective in preventing bacterial pneumonia in HIV-1-infected patients is to optimize ART (**AII**). No well-documented benefit has been

determined for secondary prophylaxis (chronic maintenance therapy) after successful completion of antibiotic treatment for bacterial respiratory tract infections.

Adults and adolescents who have a $CD4^+$ T lymphocyte count of $\geq$200 cells/microliter should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine if they have not received it during the preceding 5 years (**BII**). Annual administration of influenza vaccine might be useful in preventing pneumococcal superinfection of influenza respiratory tract infections (**BII**).

Administration of antibiotic chemoprophylaxis to HIV-1-infected patients who have frequent recurrences of serious bacterial respiratory infections should be considered (**CIII**). TMP-SMX, administered for PCP prophylaxis and clarithromycin or azithromycin, administered for MAC prophylaxis, are appropriate for drug-sensitive organisms. However, caution is required when using antibiotics solely for preventing the recurrence of serious 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 among pregnant women is the same as for nonpregnant adults, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tracts infections should be managed as in the nonpregnant adult, with certain exceptions. Clarithromycin should be avoided because of the occurrence of birth defects associated with its use among mice and rats (**DIII**). Because arthropathy has been observed among immature animals with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy and among children aged <18 years. However, >200 cases of ciprofloxacin use in pregnancy have been reported to various pregnancy registries, and its use has not been associated with arthropathy or birth defects after in utero exposure in humans. Therefore, quinolones can be used in pregnancy for drug-resistant disease when other alternatives are not available (**CIII**).

Pneumococcal and influenza vaccine can be administered during pregnancy, and influenza vaccine is recommended for all women who will be in the second or third trimester of pregnancy during the peak of influenza season (**AIII**). Because administration of vaccines might be associated with a transient rise in plasma HIV-1 RNA levels, vaccination of pregnant women is best done after ART has been initiated to minimize increases in plasma HIV-1 RNA levels that might increase the risk for perinatal HIV-1 transmission.

Bacterial Enteric Disease

Treatment Recommendations

Immunocompetent hosts without HIV-1 infection often do not require treatment for *Salmonella* gastroenteritis; the condition is self-limited and treatment might prolong the carrier state. Although no treatment trials have examined this strategy among patients with HIV-1 infection, the risk for bacteremia is sufficiently high that the majority of specialists recommend treatment of all HIV-1-associated *Salmonella* infections (**BIII**).

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone (**AIII**). Ciprofloxacin is the preferred agent (**AIII**); it is likely that other fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin) also would be effective in treatment of salmonellosis among HIV-1-infected persons, but these have not been well evaluated in clinical studies (**BIII**).

The length of therapy for HIV-1-related *Salmonella* infection is poorly defined. For mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable in an effort to reduce the risk for extraintestinal spread (**BIII**). Among patients with advanced HIV-1 disease ($CD4^+$ T lymphocyte count <200/microliter) or who have *Salmonella* bacteremia, at least 4 to 6 weeks of treatment is often recommended (**BIII**). Depending on antibiotic susceptibility, alternatives to the fluoroquinolone antibiotics for *Salmonella* spp. include TMP-SMX or expanded spectrum cephalosporins (e.g., ceftriaxone or cefotaxime) (**BIII**).

As with non-HIV-infected patients, the optimal treatment of campylobacteriosis among persons with HIV-1 infection is poorly defined. Among patients with mild disease, certain clinicians might opt to withhold therapy unless symptoms persist for more than several days. Increasing resistance to fluoroquinolones makes the choice of therapy especially problematic. For mild-to-moderate disease, initiating therapy with a fluoroquinolone (ciprofloxacin) or a macrolide (azithromycin), pending susceptibility test results, and treating for 7 days is a reasonable approach (**BIII**). Patients with bacteremia should be treated for at least 2 weeks (**BIII**), and adding a second active agent (e.g., an aminoglycoside) might be prudent (**CIII**).

Therapy for shigellosis is indicated both to shorten the duration of illness and to prevent spread of the infection to others (**AIII**). The recommended treatment is with a fluoroquinolone for 3 to 7 days (**AIII**). Alternatives to this treatment include TMP-SMX for 3 to 7 days or azithromycin for 5 days (**BIII**). Cases of *Shigella* acquired internationally have high rates of TMP-SMX resistance; in addition, HIV-1-infected persons have higher rates of adverse effects related to this agent. As a result, fluoroquinolones are preferred as first-line.

Treatment of patients who have *Shigella* bacteremia is less well defined. Depending on the severity of infection, it might be reasonable to extend treatment to 14 days, using the agents described previously (**AIII**).

Monitoring and Adverse Events

Patients should be monitored closely for response to treatment, as defined clinically by improvement in systemic signs and symptoms and resolution of diarrhea. A follow-up stool culture to demonstrate clearance of the organism is not generally required if a complete clinical response has been demonstrated but should be considered for those who fail to clinically respond to appropriate antimicrobial therapy, or when public health considerations dictate the need to ensure microbiologic cure (e.g., health-care or food service workers).

Management of Treatment Failure

Treatment failure is defined by the lack of improvement in clinical signs and symptoms of diarrheal illness and the persistence of organisms in stool, blood, or

other relevant body fluids or tissue after completion of appropriate antimicrobial therapy for the recommended duration. Certain patients with *Salmonella* bacteremia might remain febrile for 5 to 7 days despite effective therapy. Therefore, careful observation is required to determine the adequacy of the response.

Treatment should be guided by drug susceptibility testing of isolates recovered in culture. An evaluation of other factors that might contribute to failure or relapse, such as malabsorption of oral antibiotics, a sequestered focus of infection (e.g., an undrained abscess), or adverse drug reactions that interfere with antimicrobial activity, should be undertaken as indicated.

Prevention of Recurrence

HIV-1-infected persons who have *Salmonella* bacteremia should receive long-term secondary prophylaxis (chronic maintenance therapy) to prevent recurrence. Fluoroquinolones, primarily ciprofloxacin, are usually the drugs of choice for susceptible organisms (**BII**). Chronic suppressive or maintenance therapy is not generally recommended for *Campylobacter* or *Shigella* infections among persons with HIV-1 infection (**EIII**). Household contacts of HIV-1-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of *Salmonella* or *Shigella* so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission to the HIV-1-infected person can be prevented (**CIII**).

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infections among pregnant women is the same as among nonpregnant women. Bacterial enteric infections should be managed as in the nonpregnant adult, with several considerations. Because arthropathy has been observed among immature animals with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy and among children aged <18 years. Therefore, expanded spectrum cephalosporins, TMP-SMX or azithromycin, depending on the organism and the results of susceptibility testing, should generally be considered as first-line therapy (**CIII**). However, >200 cases of ciprofloxacin use in pregnancy have been reported to various pregnancy registries, and its use has not been associated with arthropathy or birth defects after in utero exposure in humans. Therefore, quinolones can be used in pregnancy for drug-resistant disease (**CIII**). Neonatal-care providers should be informed of maternal sulfa therapy if used near delivery because of the theoretical increased risk to the newborn of hyperbilirubinemia and kernicterus.

Bartonellosis

Treatment Recommendations

No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis. Erythromycin and doxycycline have been used successfully to treat bacillary angiomatosis, peliosis hepatica, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis on the basis of reported experience in case series (**AII**). Therapy should last at least 3 months (**AII**). Doxycycline is the treatment of choice for central nervous system bartonellosis

(**AIII**). Clarithromycin or azithromycin have been associated with clinical response in certain cases and are considered second line alternatives (**BII**), although treatment failures have been reported with both drugs.

The beta-lactams (penicillins and first-generation cephalosporins) have no appreciable in vitro activity and are not recommended for treatment of bartonellosis (**DII**). Quinolones have variable in vitro activity and clinical response in case reports; as a result, they are not generally recommended as first-line therapy but might be tried as second-line alternatives (**CIII**).

Management of Treatment Failure

Among patients who fail to respond to initial treatment, one or more of the second-line alternative regimens should be considered (**AIII**). Among patients who relapse, lifelong therapy is recommended (**AIII**).

Prevention of Recurrence

Relapse or reinfection with *Bartonella* has sometimes followed a course of primary treatment. Although no firm recommendation can be made about secondary prophylaxis (chronic maintenance therapy) in this setting, long-term suppression of infection with erythromycin or doxycycline should be considered (**CIII**).

Special Considerations During Pregnancy

Pregnancy has been associated with a more severe course and possible increased risk for death with acute infection caused by *B. bacilliformis* in immunocompetent patients. No data are available on the potential impact of pregnancy on *Bartonella* infections among HIV-1-infected persons. Similarly, *B. bacilliformis* infections during pregnancy might increase the risk for spontaneous abortion and stillbirth and can be transmitted to the fetus. No data are available on the effect of other *Bartonella* infections on pregnancy outcome.

Diagnosis of *Bartonella* infections in pregnant women should be the same as in nonpregnant adults. Treatment during pregnancy should be with erythromycin rather than tetracyclines because of the increased hepatotoxicity and staining of fetal teeth and bones associated with the use of tetracyclines during pregnancy (**AIII**). Cephalosporins are not recommended.

Syphilis

Treatment Recommendations

Management of HIV-1-infected patients with syphilis is similar to the management of HIV-uninfected persons with the disease. However, closer follow-up is recommended to detect potential treatment failures or disease progression. All patients with syphilis, regardless of disease stage, should be evaluated for clinical evidence of CNS or ocular involvement. Those with neurologic or ocular symptoms or signs should undergo CSF examination to rule out neurosyphilis. HIV-1-infected patients with late-latent syphilis, including those with syphilis of unknown duration, also should undergo CSF examination. Certain specialists recommend

CSF examination for all HIV-1-infected patients with syphilis, regardless of stage. Similar to the HIV-uninfected population, HIV-1-infected patients with active tertiary syphilis (i.e., aortitis and gumma) or who fail treatment for non-neurologic syphilis should undergo CSF examination. Patients with CSF abnormalities consistent with neurosyphilis should be treated for neurosyphilis.

HIV-1--infected persons with early-stage (i.e., primary, secondary, or early latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G (**AII**). Alternative therapies, including oral doxycycline, ceftriaxone, and azithromycin, have not been sufficiently evaluated in HIV-1-infected patients to warrant use as first-line treatment. If the clinical situation requires the use of an alternative to penicillin, treatment should be undertaken with close clinical monitoring (**BIII**). In a randomized clinical trial, amoxicillin administered with probenecid, which increases CSF amoxicillin levels, did not improve clinical outcome of early stage disease and is not recommended (**DII**).

In HIV-1-infected patients with late-latent syphilis for whom the CSF examination excludes the diagnosis of neurosyphilis, treatment with three weekly intramuscular injections of 2.4 million units benzathine penicillin G is recommended (**AIII**). Alternative therapy with doxycycline 100 mg by mouth twice a day for 28 days has not been sufficiently evaluated in HIV-1-infected patients to warrant use as first-line treatment. If the clinical situation requires the use of an alternative to penicillin, treatment should be undertaken with close clinical monitoring (**BIII**).

HIV-1-infected patients with clinical evidence of late-stage (tertiary) syphilis (cardiovascular or gummatous disease) should have a CSF examination to rule out neurosyphilis before initiating therapy (**AIII**). The complexity of tertiary syphilis management is beyond the scope of these guidelines and providers treating tertiary disease are advised to consult an infectious disease specialist (**AIII**).

HIV-1-infected patients with clinical or laboratory evidence of neurosyphilis (i.e., CNS involvement including otic and ocular disease, even with a normal CSF) should receive intravenous aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units intravenously (IV) every 4 hours or by continuous infusion for 10 to 14 days (**AII**) or procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10 to 14 days(**BII**). HIV-1-infected patients who are allergic to sulfa-containing medications should not be administered the IM alternative because they are very likely to be allergic to probenecid (**DIII**). IM procaine penicillin without probenecid does not achieve sufficient penicillin levels in CSF to treat neurosyphilis.

Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, certain specialists recommend following neurosyphilis treatment with 3 weeks of benzathine penicillin, 2.4 million units IM weekly. However, no consensus has been reached about the need for this practice (**CIII**). Among penicillin allergic patients, penicillin desensitization followed by one of the penicillin regimens listed previously is the preferred approach (**BIII**). However, limited data indicate that ceftriaxone (2 g daily IV for 10 to 14 days) might be an alternative regimen (**CIII**).

Monitoring and Adverse Events

Clinical and serologic responses to treatment of early stage (i.e., primary, secondary, and early-latent) disease should be monitored at 3, 6, 9, 12, and 24 months after therapy. Serologic responses to treatment might differ among HIV-1-infected patients compared with HIV-uninfected persons, including temporal pattern of response and proportion of subjects achieving serologically defined treatment success (at least a fourfold decrease in titer).

After successful treatment for syphilis among HIV-1-infected and uninfected patients, some might remain "serofast," meaning that serum nontreponemal test titers remain reactive at low and unchanging titers, generally $\leq$1:8, for extended periods of time (up to the lifetime of the patient). The clinical significance of the serofast state is unclear, but it probably does not represent treatment failure. Serologic detection of potential reinfection should be based on at least a fourfold increase in titer above the established serofast baseline.

Response to therapy of late-latent syphilis should be monitored using nontreponemal serologic tests at 3, 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer. Two retrospective studies reported that concomitant HIV-1 infection was associated with poorer CSF and serologic responses to neurosyphilis therapy. Repeat CSF examination should be performed at 3 and 6 months after completion of therapy and then every 6 months until the CSF white blood cell count is normal and the CSF-Venereal Disease Research Laboratory test (VDRL) is nonreactive. Because of the complex nature of neurosyphilis, treatment should be undertaken in consultation with an infectious disease specialist.

Management of Treatment Failure

Retreatment of patients with early stage syphilis should be considered for those who 1) do not experience at least a fourfold decrease in serum nontreponemal test titers 6 to 12 months after therapy, 2) have a sustained fourfold increase in serum nontreponemal test titers after an initial reduction after treatment, or 3) have persistent or recurring clinical signs or symptoms of disease (**BIII**). If CSF examination does not confirm the diagnosis of neurosyphilis, such patients should receive 2.4 million units IM benzathine penicillin G administered at 1-week intervals for 3 weeks (**BIII**). Certain specialists have also recommended a course of aqueous penicillin G IV or procaine penicillin IM plus probenecid, as described for treatment of neurosyphilis above, in this setting (**CIII**). If titers fail to respond appropriately after retreatment, repeat CSF evaluation or retreatment might not be beneficial (**CIII**).

Patients with late-latent syphilis should have a repeat CSF examination and be retreated if they have clinical signs or symptoms of syphilis, have a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (less than fourfold decline in nontreponemal test titer) within 12 to 24 months of therapy (**BIII**). If the CSF examination is consistent with CNS involvement, retreatment should follow the neurosyphilis recommendations (**AIII**); those without a profile indicating CNS disease should receive a repeat course of benzathine penicillin, 2.4 million units IM weekly for 3 weeks (**BIII**), although certain specialists recommend following the neurosyphilis recommendations in this setting (**CIII**). Retreatment of neurosyphilis should be

considered if the CSF WBC count has not decreased after 6 months after completion of treatment, or if the CSF-VDRL remains reactive 2 years after treatment (**BIII**).

Secondary Prevention and Maintenance Therapy

No recommendations have been developed indicating the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis in HIV-1-infected patients.

Special Considerations During Pregnancy

All pregnant women should be screened for syphilis at the first prenatal visit. In areas where syphilis prevalence is high or among women at high risk (e.g., uninsured, women living in poverty, commercial sex workers, and injection-drug users), testing should be repeated at 28 weeks of gestation and at delivery. All women delivering a stillborn infant after 20 weeks of gestation should also be tested for syphilis. Syphilis screening should also be offered at sites providing episodic care to pregnant women at high risk including emergency departments, jails, and prisons. No infant should leave the hospital without documentation of maternal syphilis serology status during pregnancy.

The rate of transmission and adverse outcomes of untreated syphilis are highest with primary, secondary, and early latent syphilis during pregnancy and decrease with increasing duration of infection thereafter. Pregnancy does not appear to alter the course, manifestations, or diagnostic test results of syphilis infection among adults. The diagnosis should be made the same as among nonpregnant adults. Concurrent syphilis infection might increase the risk for perinatal transmission of HIV-1 to the infant, although an increased risk has not been consistently reported.

Treatment during pregnancy should consist of the same penicillin regimen as recommended for the given disease stage among nonpregnant, HIV-1-infected adults. Because of treatment failures reported after single injections of benzathine penicillin among HIV-uninfected pregnant women, certain specialists recommend a second injection 1 week after the initial injection for pregnant women with early syphilis. Because of additional concerns about the efficacy of standard therapy in HIV-1-infected persons, a second injection 1 week after the first for HIV-1-infected pregnant women should be considered (**BIII**).

No alternatives to penicillin have been proven effective and safe for treatment of syphilis during pregnancy or for prevention of fetal infection. Pregnant women who have a history of penicillin allergy should be referred for skin testing and desensitization and treatment with penicillin (**AIII**). Erythromycin does not reliably cure fetal infection; tetracyclines should not be used during pregnancy because of hepatotoxicity and staining of fetal bones and teeth (**EIII**). Efficacy data with azithromycin or ceftriaxone are insufficient to support a recommendation for their use in this setting (**DIII**).

A Jarisch-Herxheimer reaction occurring during the second half of pregnancy might precipitate preterm labor or fetal distress. Consideration should be given to providing fetal and contraction monitoring for 24 hours after initiation of

treatment for early syphilis of pregnant women who are ≥20 weeks of gestation, especially in the setting of abnormal ultrasound findings indicative of fetal infection (**BIII**). Alternatively, women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement.

Repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy. Titers can be conducted monthly for women at high risk for reinfection. The clinical and antibody response should be appropriate for the stage of disease, although the majority of women will deliver before their serologic response can be definitively assessed.

Mucocutaneous Candidiasis

Treatment Recommendations

Although initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches or nystatin suspension or pastilles (**BII**), oral fluconazole is as effective and, in certain studies, superior to topical therapy and is more convenient and generally better tolerated (**AI**). Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole but less well tolerated (**AI**). Ketoconazole and itraconazole capsules are less effective than fluconazole because of their more variable absorption and should be considered second line alternatives (**DII**).

Systemic therapy is required for effective treatment of esophageal candidiasis (**AII**). A 14- to 21-day course of either fluconazole or itraconazole solution is highly effective (**AI**). As with oropharyngeal candidiasis, ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption (**DII**). Although caspofungin (**AII**) and voriconazole (**AII**) are effective in treating esophageal candidiasis among HIV-1-infected patients, experience is limited and fluconazole remains the preferred agent. Although symptoms of esophageal candidiasis might be mimicked by other pathogens, a diagnostic trial of antifungal therapy is often appropriate before endoscopy is undertaken to search for other causes of esophagitis.

Uncomplicated vulvovaginal candidiasis is observed in 90% of HIV-1-infected women and responds readily to short-course oral or topical treatment with any of several therapies including single-dose regimens (**AII**):

- Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3 to 7 days
- Topical nystatin 100,000 units daily for 14 days
- Itraconazole oral solution 200 mg twice a day for 1 day or 200 mg daily for 3 days
- Oral fluconazole 150 mg for 1 dose

Complicated vaginitis (prolonged or refractory episodes) is observed in approximately 10% of patients and requires antimycotic therapy for >7 days (**AII**).

Monitoring and Adverse Events

For the majority of patients, response to therapy is rapid, with improvement in signs and symptoms within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although patients might experience cutaneous hypersensitivity reactions, with rash and pruritis. Patients might experience gastrointestinal upset with oral azole treatment. Patients treated for >7 to 10 days with azoles might experience hepatotoxicity. If prolonged therapy is anticipated (>21 days), periodic monitoring of liver chemistry studies should be considered.

Management of Treatment Failure

Treatment failure is generally defined as signs and symptoms of oropharyngeal or esophageal candidiasis that persist for more than 7 to 14 days of appropriate therapy. Fluconazole-refractory oropharyngeal candidiasis will respond at least transiently to itraconazole solution in approximately two thirds of persons (**AII**). Amphotericin B oral suspension (1 mL four times daily of the 100 mg/mL suspension) is sometimes effective among patients with oropharyngeal candidiasis who do not respond to itraconazole (**CIII**); however, this product is not available in the United States. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease (**BII**). Fluconazole-refractory esophageal candidiasis should be treated with caspofungin (**BIII**) or intravenous amphotericin B, either conventional or liposomal or lipid complex formulations (**BII**).

Prevention of Recurrence

The majority of HIV specialists do not recommend secondary prophylaxis (chronic maintenance therapy) of recurrent oropharyngeal or vulvovaginal candidiasis because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida* organisms to develop, the possibility of drug interactions, and the cost of prophylaxis (**DIII**). However, if recurrences are frequent or severe, an oral azole, fluconazole (**CI**), or itraconazole solution (**CI**) (or for recurrent vulvovaginal candidiasis, daily prophylaxis with any topical azole [**CII**]) should be considered. Other factors that influence choices related to such therapy include impact of recurrences on the patient's well-being and quality of life, need for prophylaxis for other fungal infections, cost, toxicities, drug interactions, nutritional status, and potential to induce drug resistance among *Candida* and other fungi.

Prolonged use of systemically absorbed azoles, specifically among patients with low $CD4^+$ T lymphocyte counts (i.e., <100 cells/microliter) increases the risk for developing azole resistance. Adults or adolescents who have a history of one or more episodes of documented esophageal candidiasis should be considered candidates for secondary prophylaxis. Fluconazole 100 to 200 mg daily is appropriate (**BI**). However, potential azole resistance should be considered when long-term azoles are considered.

Special Considerations During Pregnancy

Pregnancy increases the risk for vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same as among nonpregnant adults.

Fluconazole is teratogenic in high doses in animal studies. Among humans, four cases of an unusual cluster of defects (i.e., craniofacial and skeletal) have been reported after prolonged use at high doses in the first trimester of pregnancy. Teratogenic effects have not been described among animals at doses similar to those used in humans, and anomalies do not appear to be increased among infants born to women receiving single-dose fluconazole treatment in the first trimester. Itraconazole is teratogenic among rats and mice (i.e., skeletal defects, encephalocele, and macroglossia) at high doses. Similar to fluconazole, no increase in anomalies has been noted among women exposed to treatment doses in the first trimester.

Invasive or refractory esophageal *Candida* infections should be treated the same in pregnancy as in the nonpregnant woman, with the exception that amphotericin B should be substituted for fluconazole or itraconazole (if indicated) in the first trimester if similar efficacy is to be expected (**BIII**).

Cryptococcosis

Treatment Recommendations

Untreated cryptococcal meningitis is fatal. The recommended initial treatment for acute disease is amphotericin B, usually combined with flucytosine, for a 2-week duration followed by fluconazole alone for an additional 8 weeks (**AI**). This approach is associated with a mortality of <10% and a mycologic response of approximately 70%.

The addition of flucytosine to amphotericin B during acute treatment does not improve immediate outcome but is well tolerated for 2 weeks and decreases the risk for relapse. Lipid formulations of amphotericin B appear effective. The optimal dose of lipid formulations of amphotericin B has not been determined, but AmBisome has been effective at doses of 4 mg/kg body weight/daily (**AI**).

After a 2-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole administered for 8 weeks or until CSF cultures are sterile (**AI**). Itraconazole is an acceptable though less effective alternative (**BI**). Combination therapy with fluconazole (400 to 800 mg/daily) and flucytosine is effective for treating AIDS-associated cryptococcal meningitis. However, because of the toxicity of this regimen (especially myelotoxicity and gastrointestinal toxicity), it is recommended only as an alternative option for persons unable to tolerate or unresponsive to standard treatment (**BII**).

Increased intracranial pressure might cause clinical deterioration despite a microbiologic response, probably reflects cerebral edema, and is more likely if the CSF opening pressure is >200 mm H_2O. In one large clinical trial, 93% of deaths occurring within the first 2 weeks of therapy and 40% of deaths occurring within weeks 3 to 10 were associated with increased intracranial pressure. The opening pressure should always be measured when a lumbar puncture is performed.

The principal initial intervention for reducing symptomatic elevated intracranial pressure is repeated daily lumbar punctures (**AII**). CSF shunting should be considered for patients in whom daily lumbar punctures are no longer being tolerated or whose signs and symptoms of cerebral edema are not being relieved (**BIII**). Whether reducing opening pressure leads to a reduction in the mortality and morbidity associated with cerebral edema is unknown. No role exists for acetazolamide to reduce intracranial pressure (**DIII**).

Monitoring and Adverse Events

A repeat lumbar puncture to ensure clearance of the organism is not required for those with cryptococcal meningitis and improvement in clinical signs and symptoms after initiation of treatment. If new symptoms or clinical findings occur after 2 weeks of treatment, a repeat lumbar puncture should be performed.

Serum cryptococcal antigen is not helpful in management because changes in titer do not correlate with clinical response. Serial measurement of CSF cryptococcal antigen might be more useful but requires repeated lumbar punctures and is not routinely recommended for monitoring response.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Supplemental colloidal fluids might reduce the risk for nephrotoxicity during treatment (**CIII**). Infusion-related adverse reactions (e.g., fever, chills, renal tubular acidosis, hypokalemia, orthostatic hypotension, tachycardia, nausea, headache, vomiting, anemia, anorexia, and phlebitis) might be ameliorated by pretreatment with acetaminophen, diphenhydramine, or corticosteroids administered approximately 30 minutes before the infusion (**CIII**). Lipid formulations of amphotericin B are less toxic.

Azotemic patients receiving flucytosine should have their blood levels monitored to prevent bone marrow suppression and gastrointestinal toxicity; peak serum levels (2 hours after an oral dose) should be <100 micrograms/mL. Persons treated with fluconazole should be monitored for hepatotoxicity, although this toxicity is rare.

Management of Treatment Failure

Treatment failure is defined as clinical deterioration despite appropriate therapy (assuming increased intracranial pressure is being adequately treated as described previously), the lack of improvement in signs and symptoms after 2 weeks of appropriate therapy, or relapse after an initial clinical response. A repeat lumbar puncture should be performed (if a shunt is not already in place) to ascertain whether or not intracranial pressure has increased. Although fluconazole resistance has been reported with *Cryptococcus neoformans*, it is rare. Susceptibility testing is not routinely recommended, and susceptibility techniques have not been standardized for this purpose.

The optimal therapy for those with treatment failure is not known. Those who have failed on fluconazole should be treated with amphotericin B with or without flucytosine as indicated previously, and therapy should be continued until a clinical response occurs (**BIII**). Higher doses of fluconazole in combination with

flucytosine also might be useful (**BIII**). Unlike caspofungin, voriconazole has activity against *Cryptococcus* spp. *in vitro* and might be an alternative.

Prevention of Recurrence

Patients who have completed initial therapy for cryptococcosis should be administered lifelong suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) (**AI**), unless immune reconstitution occurs as a consequence of ART. Fluconazole (**AI**) is superior to itraconazole (**BI**) for preventing relapse of cryptococcal disease and is the preferred drug.

Adult and adolescent patients appear at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained increase (i.e. $\geq$6 months) in their $CD4^+$ T lymphocyte counts to >100 to 200 cells/microliter after ART. The numbers of such patients who have been evaluated remain limited. On the basis of these observations and inference from more extensive data regarding safety of discontinuing secondary prophylaxis for other opportunistic infections during advanced HIV-1 disease, discontinuing chronic maintenance therapy among such patients is a reasonable consideration (**CIII**). Certain HIV specialists would perform a lumbar puncture to determine if the CSF is culture-negative and antigen negative before stopping therapy even if patients are asymptomatic; other specialists do not believe this is necessary. Maintenance therapy should be reinitiated if the $CD4^+$ T lymphocyte count decreases to <100 to 200 cells/microliter (**AIII**).

Special Considerations During Pregnancy

Diagnosis and treatment for cryptococcosis among HIV-1-infected pregnant women are the same as for nonpregnant women. Considerations about the use of amphotericin B, fluconazole, and itraconazole are the same as those for mucocutaneous and invasive candidiasis (i.e., amphotericin B should be used in the first trimester to avoid the potential for teratogenicity with fluconazole or itraconazole).

Flucytosine is teratogenic in rats at high doses, but not at doses similar to human exposure. No reports exist about its use in the first trimester of pregnancy in humans. Flucytosine might be metabolized to 5-fluoruracil. It should be used in pregnancy only if clearly indicated.

Histoplasmosis

Treatment Recommendations

Patients with severe disseminated histoplasmosis who meet one or more selected criteria (temperature >102 degrees F [>39 degrees C], systolic blood pressure <90 mm Hg, pO_2 <70 torr, weight loss >5%, Karnofsky performance score <70, hemoglobin <10 g/dL, neutrophil count <1000 cells/microliter, platelet count <100,000 cells/microliter, aspartate aminotransferase >2.5 times normal, bilirubin or creatinine >2 times normal, albumin <3.5 g/dL, coagulopathy, presence of other organ system dysfunction, or confirmed meningitis) should be

treated with intravenous amphotericin B, either the deoxycholate formulation or liposomal amphotericin B, for the first 3 to 10 days until they clinically improve (**AI**). In a randomized clinical trial, liposomal amphotericin B was more effective than the standard deoxycholate formulation, inducing a more rapid and more complete response, lowering mortality, and reducing toxicity (**BI**). Intravenous itraconazole 200 mg/day after an initial higher dose induction period might be used for persons who cannot tolerate amphotericin B (**BIII**).

Patients responding well after completion of initial amphotericin B therapy for 3 to 10 days might be switched to oral therapy with itraconazole capsules to complete 12 weeks of treatment and then placed on maintenance treatment (**AII**). Itraconazole solution would be logical to use, but no trials document efficacy and tolerability in this setting. Fluconazole 800 mg daily is less effective than itraconazole, but is recommended as an alternative if patients cannot tolerate itraconazole (**CII**).

For persons with confirmed meningitis, amphotericin B should be continued for 12 to 16 weeks, followed by maintenance therapy (**AII**). Fluconazole has been recommended previously among HIV-1-uninfected persons with meningitis following amphotericin B; however, because of the data documenting efficacy of itraconazole in persons with HIV-1 disease and nonmeningeal histoplasmosis, itraconazole should be used in this setting (**AII**). Among persons with mild illness, therapy with itraconazole capsules for 12 weeks is recommended (**AII**).

Acute pulmonary histoplasmosis in an HIV-1-infected patient with intact immunity, as indicated by a $CD4^+$ T lymphocyte count >500 cells/microliter, might not require therapy and should be managed in a similar way to infection in an otherwise noncompromised host (**AIII**).

Prevention of Recurrence

Patients who complete initial therapy for histoplasmosis should be administered lifelong suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) with itraconazole 200 mg twice daily (**AI**). Certain specialists recommend serum levels be tested to ensure free itraconazole concentrations of at least 1 microgram/mL or free plus hydroxylated metabolite of 2 microgram/mL. The metabolite also has antifungal activity.

Although patients might be at low risk for recurrence of systemic mycosis when their $CD4^+$ T lymphocyte counts increase to >100 cells/microliter in response to ART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue secondary prophylaxis in this setting.

Special Considerations During Pregnancy

Treatment is the same as for nonpregnant adults. Because fluconazole is teratogenic in high doses in animal studies and itraconazole is teratogenic in high doses among rats and mice, as with other invasive fungal infections, amphotericin B should be substituted for itraconazole or fluconazole (if indicated) in the first trimester (**BIII**).

Coccidioidomycosis

Treatment Recommendations

For nonmeningeal pulmonary or disseminated disease, amphotericin B is the preferred initial therapy (**AII**). Data evaluating lipid formulations of amphotericin B are limited such that appropriate dosing recommendations cannot be made.

Therapy with amphotericin B should continue until clinical improvement is observed, which usually occurs after administration of 500 to 1,000 mg. Certain specialists would use an azole antifungal concurrently with amphotericin B (**BIII**). Fluconazole or itraconazole might be appropriate alternatives for patients with mild disease (**BIII**).

Coccidioidal meningitis should be treated with fluconazole, which has been reported to be successful in approximately 80% of patients with *Coccidioides immitis* meningitis (**AII**). Treatment for patients with meningeal disease requires consultation with a specialist. Intrathecal amphotericin B is the most accepted alternative but is toxic (**CIII**).

Prevention of Recurrence

Patients who complete initial therapy for coccidioidomycosis should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) using either fluconazole 400 mg daily or itraconazole 200 mg twice daily (**AII**). Although patients might be at low risk for recurrence of systemic mycosis when their $CD4^+$ T lymphocyte counts increase to >100 cells/microliter in response to ART, the numbers of patients who have been evaluated are insufficient to warrant a recommendation to discontinue secondary prophylaxis in this setting.

Special Considerations During Pregnancy

Coccidioides infections appear to be more likely to disseminate if acquired during pregnancy among HIV-uninfected women, with the risk increasing with increasing gestational age. This increased risk might be related to the agonistic effect of estradiol and progesterone, both found at high levels during pregnancy, on the growth of *C. immitis*. The risk for dissemination among HIV-1-infected pregnant women has not been evaluated. Invasive fungal infections should be treated the same in pregnancy as in the nonpregnant woman, with the exception that amphotericin B is the preferred agent in the first trimester because of the potential teratogenic risks of the azoles if efficacy is expected to be superior or similar to that of the azoles (**BIII**).

Aspergillosis

Treatment Recommendations

The recommended treatment for invasive aspergillosis is voriconazole. Amphotericin B, either conventional or lipid formulations, in doses equivalent to 1 mg/kg body weight/daily of standard amphotericin B is an alternative regimen

(**AIII**). Voriconazole has not been studied in this patient population. Caspofungin is approved for patients failing to tolerate or improve with standard therapy; however, it has not been studied in this patient population.

Monitoring and Adverse Events

Patients should be monitored for adverse effects related to amphotericin B. Airway obstruction can result from extensive pseudomembrane formation in those with tracheitis. Pulmonary infarction and progressive interstitial pneumonitis can lead to respiratory failure.

Management of Treatment Failure

The overall prognosis is poor among patients with advanced immunosuppression and in the absence of effective ART. Treatment failure is generally defined as failure to respond to initial therapy or progression of clinical signs and symptoms despite appropriate therapy.

No data are available to guide recommendations for the management of treatment failure. If amphotericin B was used initially, substitution with voriconazole might be considered; the alternative approach would be rational for those who began therapy with voriconazole (**BIII**).

Prevention of Recurrence

No data are available to base a recommendation for or against chronic maintenance or suppressive therapy among those who have successfully completed an initial course of treatment (**CIII**).

Special Considerations During Pregnancy

As with other invasive fungal infections, aspergillosis should be treated the same in pregnancy as in the nonpregnant adult, with the exception that amphotericin B is the preferred agent in the first trimester because of the potential teratogenic risks for the azoles, if efficacy is expected to be superior or similar to that of the azoles (**BIII**).

Cytomegalovirus (CMV) Disease

Treatment Recommendations

The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment (**AIII**). Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis (**AI**).

The ganciclovir intraocular implant plus oral valganciclovir is superior to once daily intravenous ganciclovir (and presumably to once-daily oral valganciclovir) for

preventing relapse of retinitis (**AI**). For this reason, certain HIV specialists recommend the intraocular implant plus valganciclovir as the preferred initial therapy, particularly for patients with immediately sight-threatening lesions (adjacent to the optic nerve or fovea); others prefer oral valganciclovir alone (**BII**).

Among patients with peripheral lesions that are not immediately sight-threatening, oral valganciclovir is preferable to the ganciclovir intraocular implant, intravenous ganciclovir, or intravenous foscarnet (**AII**) because of its greater ease of administration and lack of surgical or catheter-associated complications. However, any of the treatment regimens can be chosen because epidemiologic studies and clinical trials have not demonstrated substantially reduced rates of loss of visual acuity among patients treated with the ganciclovir implant compared with those treated with systemic therapies (**AII**).

Certain clinicians would not treat small peripheral CMV retinitis lesions if ART is to be initiated soon because immune recovery might ultimately control the retinitis. However, immune recovery uveitis might be more common among patients given less aggressive anti-CMV therapy. Therefore, treatment of CMV retinitis until sufficient immune recovery occurs (i.e., $CD4^+$ T lymphocyte count >100 cells/microliter for 3 to 6 months) is still preferred (**AIII**).

For therapy of colitis or esophagitis, the majority of specialists would treat with intravenous ganciclovir or foscarnet (or with oral valganciclovir if symptoms are not severe enough to interfere with oral absorption) for 21 to 28 days (**BII**) or until signs and symptoms have resolved. Certain HIV specialists would withhold therapy unless moderate to severe symptoms justify the use of systemic treatment (**BIII**) if ART is soon to be initiated or can be optimized. Treatment should be considered for persons with histologic evidence of CMV pneumonitis who do not respond to treatment of other pathogens (**AIII**).

For neurological disease, initiating therapy promptly is critical for an optimal clinical response. Although combination treatment with ganciclovir and foscarnet might be preferred as initial therapy to stabilize disease and maximize response (**BII**), this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease if ART can be optimized is unknown.

Studies are underway to evaluate the utility of preemptive therapy with systemic treatment among patients with CMV viremia and no evidence of organ system disease. Until such studies are completed, treatment of CMV viremia in the absence of organ system involvement is not recommended (**DIII**).

No data are available to demonstrate that starting ART among treatment-naïve patients with CMV retinitis would have an adverse effect on retinitis, gastrointestinal disease, or pneumonitis, or worsen immune recovery uveitis if this occurs. Therefore, no reason exists to delay initiation of appropriate ART, which should be administered to those with acute CMV retinitis, gastrointestinal disease, or pneumonitis (**BIII**). Although, no data indicate that immune recovery inflammatory reactions worsen CMV neurologic disease syndromes, because of the localized morbidity that might occur with such an inflammatory reaction, a brief delay in initiation of ART in this setting until clinical improvement occurs might be prudent (**CIII**).

Monitoring and Adverse Events

Management of CMV retinitis requires close monitoring by an experienced ophthalmologist and the primary clinician. Dilated indirect ophthalmoscopy should be performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, 1 month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment (**AIII**). Monthly fundus photographs, using a standardized photographic technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse (**AIII**).

Adverse effects of ganciclovir include neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Adverse effects of foscarnet include anemia, nephrotoxicity, electrolyte abnormalities, and neurologic dysfunction. Seizures have been reported with both ganciclovir and foscarnet. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter (**AIII**). Cidofovir is associated with dose-related nephrotoxicity and hypotony. For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected.

Immune recovery uveitis is an immunologic reaction to CMV characterized by inflammation in the anterior chamber or vitreous in the setting of immune recovery after initiation of ART and is generally observed among those with a substantial rise in $CD4^+$ T lymphocyte counts in the 4 to 12 weeks after initiation of ART. Ocular complications of uveitis include macular edema and the development of epiretinal membranes, which can cause loss of vision. Treatment usually requires periocular corticosteroids or short courses of systemic corticosteroids. Estimated response rates are approximately 50%.

Management of Treatment Failure

For patients without immune recovery after initiation of ART and who are receiving chronic maintenance therapy with systemic anti-CMV drugs, relapse of retinitis is likely to occur over time. Although drug resistance might be responsible for some episodes of relapse, early relapse is most often caused by the limited intraocular penetration of systemically administered drugs. Because it results in greater drug levels in the eye, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment (IV ganciclovir or oral valganciclovir) is generally recommended and often will control the retinitis for 6 to 8 months until the implant requires replacement (**BIII**).

Reinduction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time, and the majority of specialists recommend this approach for initial treatment of relapsed disease (**AII**). Changing to an alternative drug at the time of first relapse typically does not result in superior control of the retinitis but should be considered if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent (**AIII**). Combination ganciclovir and foscarnet are generally superior to systemic therapy with either agent alone for

patients with relapsed retinitis but is accompanied by greater toxicity; this approach might be considered for patients who are not candidates for other alternatives (**BI**).

Drug resistance occurs among patients receiving long-term therapy. Reported rates typically are <10% during the first 3 months of therapy but increase to 25 to 30% by 9 months of therapy. Reported rates are similar for ganciclovir, foscarnet, and cidofovir. 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. Resistance to foscarnet and resistance to cidofovir each occur because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir is frequently associated with cross-resistance to cidofovir and occasionally to foscarnet.

Although early relapse is generally not a result of resistance, later relapse often is. Because patients with resistant CMV nearly always have mutations in the CMV UL97 gene, and because a limited number of mutations produce the majority of cases of resistance, resistance testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay might be reasonable for patients who relapse on therapy. Although this approach also has not been validated, certain specialists would recommend performance of resistance testing using this technique, if available, to guide therapy in those with repeated relapses of CMV disease (**CIII**).

Patients with low-level ganciclovir-resistant isolates in the eye might respond to a ganciclovir implant because of the higher local levels of ganciclovir resulting from this form of therapy. However, patients with high-level ganciclovir resistant isolates typically will not respond and will require a switch to alternative therapy. Repetitive intravitreous injections of fomivirsen can be used for relapsed retinitis (**BI**) but should be combined with systemic therapy (**AI**).

Prevention of Recurrence

After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life (**AI**), unless immune reconstitution occurs as a result of ART. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral or oral ganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant or repetitive intravitreous injections of fomivirsen (**AI**). Oral valganciclovir has been approved by FDA for both acute induction therapy and for maintenance therapy, although published data are limited.

Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir have been effective for secondary prophylaxis of CMV retinitis in uncontrolled case series. Intraocular therapy alone does not provide protection to the contralateral eye or to other organ systems and typically is combined with oral valganciclovir.

The choice of a chronic maintenance regimen for patients treated for CMV disease should be made in consultation with a specialist. For patients with retinitis, this decision should be made in consultation with an ophthalmologist and should take

into consideration the anatomic location of the retinal lesion, vision in the contralateral eye, the immunologic and virologic status of the patient, and the patient's response to ART.

Patients with immediately vision-threatening lesions need prompt anti-CMV therapy because progression of the retinitis can occur during the time in which immune recovery is occurring. Daily oral ganciclovir is less effective than daily intravenous ganciclovir for maintenance therapy and with the availability of oral valganciclovir should no longer be used (**DIII**). Patients with immediately sight-threatening retinitis still might benefit most from the use of the ganciclovir implant and its superior ability to control retinitis progression (**BIII**). However, replacement of the ganciclovir implant at 6 to 8 months might not be necessary for those with sustained immune recovery. If the ganciclovir implant is used, it should be combined with oral valganciclovir until immune recovery occurs (**BIII**).

Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if relapses occur (**BII**). A role for maintenance therapy for CMV pneumonitis has not been established (**CIII**).

Discontinuing secondary prophylaxis (chronic maintenance therapy) should be considered for patients with a sustained ($\geq$ 6 months) increase in $CD4^+$ T lymphocyte counts >100 to 150 cells/microliter in response to ART (**BII**). Such decisions should be made in consultation with an ophthalmologist and should take into account such factors as magnitude and duration of $CD4^+$ T lymphocyte increase, anatomic location of the retinal lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring (**BII**). All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for immune recovery vitritis/uveitis (**AIII**).

Relapse of CMV retinitis occurs among patients whose anti-CMV maintenance therapies have been discontinued and whose $CD4^+$ T lymphocyte counts have decreased to <50 cells/microliter. Therefore, reinstitution of secondary prophylaxis should occur when the $CD4^+$ T lymphocyte count has decreased to <100 to 150 cells/microliter (**AIII**). Relapse has been reported among patients whose $CD4^+$ T lymphocyte counts are >100 cells/microliter, but such reports are rare. Because of the potential for rapid relapse of retinitis when $CD4^+$ T lymphocyte counts decline and the potential for rapid decline of $CD4^+$ T lymphocyte counts with interruption of ART, patients with immune reconstitution not receiving CMV maintenance therapy should still undergo ophthalmologic monitoring (**BIII**).

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for the nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for those in nonpregnant HIV-1-infected adults (**AIII**). For retinal disease, use of intraocular implants or intravitreous injections for local therapy should be considered in pregnancy if possible to limit fetal exposure to systemically administered antiviral drugs (**CIII**). Close ophthalmologic monitoring must be maintained, and systemic therapy should then be added as indicated after delivery.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits. Safe use in human pregnancy after organ transplantation has been reported. On the basis of very limited data and weighing toxicity of the various drugs, ganciclovir is the treatment of choice during pregnancy (**BIII**). No experience has been reported with the use of valganciclovir in human pregnancy. 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.

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. Because primary toxicity is renal, monitoring of amniotic fluid volumes by ultrasound is recommended weekly after 20 weeks of gestation to detect oligohydramnios. Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use in human pregnancy has been reported.

Rarely, ultrasound findings in the fetus (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel) might indicate the possibility of in utero CMV infection among pregnant women with CMV end organ disease. In this case, consideration of invasive testing (i.e., amniocentesis and fetal umbilical blood sampling) must be individualized based on clinical history and serologic findings, gestational age, potential risk for HIV-1 transmission, and maternal preference. Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

On the basis of data in HIV-uninfected women, transmission of CMV from mother to infant might occur in utero. However, symptomatic infection in the newborn is usually related to primary CMV infection in the mother during pregnancy, and because >90% of HIV-1-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is low. Therefore, treatment of maternal CMV infection, if asymptomatic, during pregnancy solely to prevent infant infection is not indicated (**DIII**).

Herpes Simplex Virus (HSV) Disease

Treatment Recommendations

Orolabial lesions can be treated with oral famciclovir, valacyclovir, or acyclovir for 7 days (**AII**). Moderate-to-severe mucocutaneous HSV lesions are best treated initially with intravenous acyclovir (**AII**). Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Initial or recurrent genital HSV should be treated with oral famciclovir, valacyclovir, or acyclovir for 7 to 14 days (**AII**). Trifluridine is the treatment of choice for herpes keratitis, one drop onto the cornea every 2 hours, not to exceed 9 drops/day; it is not recommended for longer than 21 days (**AII**). Intravenous acyclovir, 10 mg/kg body weight every 8 hours for 14 to 21 days, is required for HSV encephalitis (**AII**).

Monitoring and Adverse Events

Famciclovir, valacyclovir, and acyclovir might occasionally be associated with nausea, vomiting, and diarrhea. Rarely, patients receiving higher doses of valacyclovir or acyclovir might experience renal dysfunction. For patients receiving high-dose IV acyclovir, monitoring of renal function is recommended at initiation of treatment, and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction or those receiving prolonged therapy. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome resulting in death has been reported among HIV-1-infected patients treated with high-dose valacyclovir but has rarely been reported at conventional doses among persons with HIV-1 disease.

Management of Treatment Failure

Treatment failure related to resistance to antiviral drugs should be suspected if lesions do not indicate signs of resolution within 7 to 10 days after initiation of therapy. Among immunocompromised patients with suspected acyclovir-resistant HSV, a lesion culture should be obtained and, if virus is isolated, susceptibility testing performed to confirm drug resistance.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI**). Topical trifluridine or cidofovir also has been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.

Prevention of Recurrence

Chronic therapy with acyclovir is not required after lesions resolve. However, persons who have frequent or severe recurrences can be administered daily suppressive therapy with oral acyclovir, oral famciclovir, or oral valacyclovir (**AI**). Intravenous foscarnet or cidofovir can be used to treat infection caused by acyclovir-resistant isolates of HSV, which are routinely resistant to ganciclovir (**AII**).

Special Considerations During Pregnancy

Diagnosis of mucocutaneous and visceral HSV infections is the same in pregnancy as among nonpregnant adults. Treatment of visceral and symptomatic mucocutaneous HSV infections and suppressive therapy for frequent recurrences should be offered during pregnancy as they would be for nonpregnant women (**AIII**). Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe. Acyclovir is the first choice for therapy of HSV infections in pregnancy (**AIII**). Valacyclovir is the prodrug of acyclovir. Although experience with use of this drug in pregnancy is limited, its safety profile is expected to be similar to acyclovir.

Famciclovir was not teratogenic in animal studies but experience with use during human pregnancy is limited. Exposures to this drug during pregnancy should be reported to the Famciclovir Registry (888-669-6682). Because of potential teratogenicity and toxicity, foscarnet should be reserved for severe

mucocutaneous or visceral HSV infections that have failed to respond to high dose acyclovir, valacyclovir, or famciclovir.

An additional concern with HSV during pregnancy is the potential for transmission to the fetus and neonate. The rate of transmission to the fetus and neonate among HIV-1-infected pregnant women coinfected with HSV is not known. Although isolated cases of in utero transmission with primary infection during pregnancy among HIV-uninfected women have been reported, the predominant risk, regardless of HIV-1 coinfection, is from maternal genital shedding at delivery. Cesarean delivery is recommended for women with a prodrome or visible HSV genital lesions at the onset of labor (**BIII**).

Use of acyclovir in late pregnancy suppresses genital herpes outbreaks and shedding in late pregnancy among HIV-seronegative women and might reduce the need for Cesarean delivery for recurrent HSV. However, the safety and efficacy of this strategy has not been evaluated among HIV-1-infected women who are more likely to have antibody to HSV-2 and to have both symptomatic and asymptomatic reactivation of genital HSV. Therefore, the use of acyclovir specifically to reduce the need for Cesarean delivery among HIV-1-infected women is not recommended (**DIII**).

Varicella Zoster Virus (VZV) Disease

Treatment Recommendations

The recommended treatment for localized dermatomal herpes zoster is famciclovir or valacyclovir for 7 to 10 days (**AII**). If cutaneous lesions are extensive or if clinical evidence of visceral involvement is observed, intravenous acyclovir should be initiated and continued until cutaneous lesions and visceral disease are clearly resolving (**AII**). Because of its immunosuppressive effects and the absence of data to support benefit with its use in this patient population, adjunctive corticosteroid therapy to prevent postherpetic neuralgia is not recommended (**DIII**).

Progressive outer retinal necrosis is rapidly progressive and leads to profound loss of vision. Because of the rapidity of disease progression, recommended treatment is high-dose intravenous acyclovir in combination with foscarnet (**AIII**). Acute retinal necrosis typically responds to IV acyclovir, followed by oral valacyclovir (**CIII**). Concomitant laser retinal photocoagulation might be needed to prevent retinal detachments.

Intravenous acyclovir for 7 to 10 days is the recommended initial treatment for immunocompromised adults and adolescents with chickenpox (**AIII**). Switching to oral therapy after the patient has defervesced if no evidence of visceral involvement exists might be permissible (**AII**). Oral acyclovir is the recommended treatment (20 mg/kg body weight up to a maximum dose of 800 mg four times daily), but valacyclovir or famciclovir would be reasonable alternatives (**BII**).

Monitoring and Adverse Events

Recommendations are the same as for HSV.

Management of Treatment Failure

Treatment failure caused by drug resistance should be suspected if lesions do not indicate signs of resolution within 10 days of initiation of therapy or if they evolve to a verrucous appearance. A lesion culture should be obtained, and if virus is isolated, susceptibility testing performed to confirm antiviral drug resistance and to support the need for intravenous therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with intravenous foscarnet is the recommended alternative therapy (**AI**).

Prevention of Recurrence

No drug has been proven to prevent the recurrence of zoster (shingles) among HIV-1-infected persons.

Special Considerations During Pregnancy

Diagnosis of zoster and chickenpox during pregnancy is the same as among nonpregnant adults. Treatment of zoster during pregnancy should be the same as for nonpregnant women. Oral valacyclovir therapy is the preferred treatment for HIV-1-infected pregnant women who experience chickenpox during pregnancy (**BI**). Intravenous acyclovir should be used if parenteral therapy is indicated the same as for nonpregnant adults with varicella (**BI**). Women should be monitored closely for signs of pneumonitis or other systemic manifestations and hospitalized for observation and potential administration of intravenous acyclovir for any respiratory symptoms or signs of severe disease.

HIV-seronegative women with primary VZV infection (i.e., chickenpox) during pregnancy have a 0.4% risk for transmitting infection resulting in congenital varicella syndrome in the infant when infection occurs at or before 12 weeks of gestation. The risk increases to 2.2% with infection at 13 to 20 weeks, and is negligible after 20 weeks. Specific risks among HIV-1-infected women with primary VZV infection during pregnancy have not been reported. Women with primary VZV 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. Provision of varicella zoster immune globulin (VZIG) does not alter the risk of congenital varicella syndrome.

Infants born to women who have chickenpox anytime from 5 days before through 2 days after delivery should receive VZIG to reduce the severity and mortality rate of neonatal infection acquired during maternal viremia (**AII**). The maternal care provider should notify the infant's medical provider immediately of the onset of maternal chickenpox during the peripartum period.

Human Herpesvirus (HHV)-8 Disease

Treatment Recommendations

Although ganciclovir, foscarnet, and cidofovir have in vitro activity against HHV-8, and limited studies indicate these agents might be associated with reduced 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. Potent ART that suppresses HIV-1 replication reduces the frequency of occurrence of Kaposi sarcoma among HIV-1-infected persons and should be considered for all persons who qualify for such therapy (**BII**).

Prevention of Recurrence

Effective suppression of HIV-1 replication with ART among HIV-1-infected patients with Kaposi sarcoma might prevent Kaposi sarcoma progression or occurrence of new lesions and should be considered for all persons with evidence of active Kaposi sarcoma (**BII**).

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among HIV-1-infected pregnant women varies widely 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 four other U.S. cities. Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels. HHV-8 seropositivity does not appear to impact pregnancy outcome. Routine screening for HHV-8 by polymerase chain reaction (PCR) or serology is not indicated for pregnant women.

Diagnosis of Kaposi sarcoma or other HHV-8-associated neoplasms in pregnancy should be the same as among nonpregnant women. Recommendations for the treatment of HHV-8 malignancies are beyond the scope of this report. Treatment should be undertaken in consultation with a specialist.

Perinatal transmission of HHV-8 occurs but appears to be infrequent. A study of 32 mother-infant pairs indicated that maternal HHV-8 infection might increase the risk for perinatal transmission of HIV-1, although no evidence of HHV-8 infection was identified among HIV-1-infected infants. Data indicate increased mortality through 24 months among HIV-1-infected infants born to HHV-8 seropositive compared with HHV-8 seronegative mothers. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of Kaposi sarcoma developing shortly after birth, higher risk for transmission with higher maternal antibody titer (and by inference higher HHV-8 viral titers), and detection of HHV-8 DNA by PCR in specimens drawn at birth from infants born to HHV-8 seropositive mothers. The majority of studies demonstrate a rate of persistent antibody positivity in children of 2 to 29% by age 4 years with the majority of studies documenting a substantially higher rate of seropositivity among children born to HHV-8 antibody positive compared with antibody negative women.

Progressive Multifocal Leukoencephalopathy (PML) Caused by JC Virus

Treatment Recommendations

No effective therapy for JC virus exists. Randomized clinical trials have evaluated vidarabine and cidofovir; neither is effective in producing clinical improvement and neither is recommended (**EI**). When ART is initiated and $CD4^+$ T lymphocyte counts rise, certain patients will experience neurologic improvement and others might become neurologically stable. However, reports have documented patients

experiencing worse neurologic manifestations after initiation of ART. In certain instances, this worsening is caused by an immune reconstitution inflammatory syndrome; other cases represent the natural history of PML.

Prevention of Recurrence

No role exists for antiviral agents in the prevention of recurrence or progression of PML.

Human Papillomavirus Disease (HPV)

Treatment Recommendations

Treatments are available for genital warts, but none is uniformly effective. The rate of recurrence is high with most modalities. Data are limited on the response of HIV-1-infected patients to the available treatments for genital warts. In the absence of data specific to the HIV-1--infected population, guidelines for the treatment of sexually transmitted diseases should be followed. Data are insufficient to recommend a single treatment modality for all patients, and more than one treatment option might be required for refractory or recurrent lesions among patients with HIV-1 infection.

Patient-applied treatments are generally recommended for uncomplicated external lesions, and consist of the following options (**CIII**):

- Podofilox is an antimitotic agent that should be applied topically to wart lesions as a 0.5% solution or a 0.5% gel; twice daily applications for 3 consecutive days can be repeated weekly for up to 4 weeks (**BIII**). The efficacy is 40 to 60% in immunocompetent subjects.
- Imiquimod is a topical cytokine inducer that recruits an inflammatory response to the site of the wart. A 5% cream formulation is applied to lesions at bedtime and removed in the morning by washing. The drug should be applied on three nonconsecutive nights/week for up to 16 weeks (**BII**). The efficacy of imiquimod in immunocompetent persons is 30 to 70%; the overall response in HIV-1 seropositive persons might be lower than in immunocompetent persons.

Provider-applied treatments are generally recommended for complex or multicentric lesions or those lesions inaccessible to patient-applied treatments (**CIII**). Options are summarized as follows:

- Cryotherapy with liquid nitrogen should be applied until each lesion is thoroughly frozen. Certain specialists recommend allowing the lesion to thaw and freezing a second time in each session. Cryotherapy sessions can be repeated every 1 to 2 weeks up to 3 to 4 times (**BIII**). The efficacy of cryotherapy is 60 to 80%.
- Trichloroacetic or bichloroacetic acids act as caustic agents to kill wart tissue. They can be made in an 80 to 95% aqueous solution and applied to each lesion. The treatment can be repeated weekly for 3 to 6 weeks (**BIII**). The expected efficacy is 60 to 80%.

- Surgical treatments include excision by scissor, shave, or curette or by electrosurgery (**BIII**). Laser surgery can also be used, but is generally more expensive (**CIII**). The efficacy of surgical removal can approach 100% depending on the location of the lesions.
- Topical application of cidofovir has reported activity against genital warts in limited, uncontrolled studies (**CIII**). No topical formulation is commercially available.
- Podophyllin resin is a crude extract that contains podophyllotoxin and other cytotoxins and induces wart necrosis after topical application. It is prepared as a 10 to 25% suspension in tincture of benzoin. It is applied by the provider to all lesions (up to 10 cm^2 of skin area) and then removed by washing a few hours later. Applications can be repeated weekly for 3 to 6 weeks (**CIII**). Efficacy ranges from 20 to 80%.
- Intralesional interferon is not generally recommended because of its high cost, difficult administration, and potential for systemic side effects (i.e., fever, fatigue, myalgias, and leukopenia) (**DIII**). The overall efficacy of interferon is no better than other therapies, and it has not been specifically studied for genital warts among HIV-1-infected persons.

The management of cervical intraepithelial neoplasia (CIN) among HIV-1-infected patients should not differ from recently published guidelines (**AIII**). The majority of specialists recommend observation without specific intervention for CIN 1 unless lesions persist over an 18 to 24 month period of follow-up, evolve to CIN 2 or worse, or there is poor adherence to routine monitoring. Conventional therapies used for treatment of CIN 2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). LEEP is generally the preferred mode of treatment (**BIII**). Recurrence rates of 40 to 60% after treatment have been reported among HIV-1-infected women undergoing these procedures.

For anal intraepithelial neoplasia (AIN), data are insufficient to recommend a specific treatment approach; because the majority of lesions are not visible to the patient, the majority of specialists recommend use of one or more of the provider-applied treatments outlined previously (**CIII**) (see Table 4, titled "Treatment of anal intraepithelial neoplasia [AIN]," in the original guideline document). Treatment decisions are based on assessment of the size and location of the lesion and the grade of histology. The least aggressive approaches should be tried first whenever possible (**CIII**). If a lesion is too large or if treatment is expected to produce substantial morbidity, then certain specialists recommend following patients without treatment and periodic examinations to monitor for development of cancer. A study reported a low success rate for surgical fulguration of widespread AIN 2 or 3 among HIV-1--infected persons. No indications exist for radiation therapy for patients with AIN in the absence of evidence of invasive cancer (**EIII**).

The results of studies 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 for the purpose of treating CIN or AIN (**CIII**), although limited data indicate that ART might be associated with improved response rates.

Monitoring and Adverse Effects

As efficacy varies with each of the treatments for genital warts, and recurrences are common, patients should be monitored by physical examination for evidence of recurrence. The major toxicity of podofilox and topical podophyllin is local skin irritation. Also, if podophyllin is applied to a large treatment area, systemic absorption can cause nausea, vomiting, and CNS effects. The major toxicity of imiquimod is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major side effects of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major adverse events associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional interferon is associated with systemic toxicities of interferon, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms.

For patients with CIN 1 that has not been treated with one of the outlined interventions, Pap smears or colposcopy should be performed every 4 to 6 months to monitor for persistence or progression of lesions. As the recurrence of CIN and cervical cancer after conventional therapy is increased among HIV-1-infected persons, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination when indicated according to published guidelines.

Management of Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. If evidence exists of persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed (**AIII**). For persistent or recurrent CIN 2 or 3, repeat loop excision or one or more of the other treatment modalities should be considered (**AIII**).

Prevention of Recurrence

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts. Patients with CIN should be monitored with frequent cytologic screening and, when indicated, colposcopic examination for recurrent lesions (**AI**). In a study of HIV-1-infected women treated for high-grade cervical lesions using conventional therapies, low-dose intravaginal 5-fluorouracil (i.e., 2 g twice weekly for 6 months) reduced the short-term risk for recurrence and possibly the grade of recurrence. However, clinical experience with this therapy is too limited to provide a recommendation for its use (**CIII**).

Special Considerations During Pregnancy

The decision about whether to treat genital warts during pregnancy should be individualized on the basis of the extent of the warts, concurrent symptoms, gestational age, and patient preference (**CIII**). Podophyllin and podofilox should not be used during pregnancy (**EIII**). Use of podophyllin has been associated with an increased risk for fetal death in several animal models and case reports in humans, but not with congenital anomalies. No experience with imiquimod in human pregnancy has been reported; therefore, its use in pregnancy is not

recommended (**DIII**). No anomalies have been observed among animals with use during pregnancy.

Other topical treatments (e.g., bichloroacetic and trichloroacetic acid) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy. Cervical warts should be biopsied to rule out concomitant dysplasia. Increased bleeding might occur with cervical biopsy during pregnancy.

All pregnant women should have a Pap smear at their initial prenatal visit unless a normal cervical cytology result has been obtained within the past year. Cytobrush sampling can be done during pregnancy. Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of any abnormalities. Increased bleeding might occur with cervical biopsy during pregnancy. Endocervical curettage should not be done during pregnancy (**DIII**).

Repeat cytology with or without colposcopy should be conducted at 34 to 36 weeks of gestation to rule out progression of dysplasia. Women with any grade of cervical dysplasia can deliver vaginally (if otherwise appropriate based on obstetrical and HIV parameters) with repeat colposcopy and definitive therapy completed postpartum. Women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and delivery planning because vaginal delivery is not recommended with invasive cervical cancer.

Pregnancy appears to increase the rate of detection of genital HPV DNA among HIV-uninfected women and might be associated with an increased frequency and rate of growth of genital warts. The effect of pregnancy on genital HPV detection among HIV-1-infected women has not been evaluated.

Transmission of genital HPV type 6 and 11 from vaginal secretions at delivery is the presumed mechanism of early onset recurrent laryngeal papillomatosis in infants. Although rare, this condition occurs more frequently among infants delivered vaginally compared with those delivered by Cesarean section. No change in obstetrical management is indicated for women with HPV infection unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding.

Hepatitis C Virus (HCV) Disease

Treatment Recommendations

Because of the scarcity of published experience treating HIV-1/HCV coinfected persons, practice is dictated largely by principles established for the treatment of HIV-uninfected persons. All patients with chronic hepatitis C should be counseled to avoid alcohol consumption because of the potential increased risk for fibrotic progression.

Because fulminant hepatic failure from hepatitis A virus infection occurs at increased frequency in persons with chronic liver disease, persons susceptible to hepatitis A virus (HAV) should receive 2 doses of HAV vaccine (**BIII**). HAV vaccine should be administered before the $CD4^+$ T lymphocyte count declines to

<200 cells/microliter because the response will probably be better. In addition, susceptible HIV-1-infected persons at risk for hepatitis B virus (HBV) infection should receive the hepatitis B vaccine series.

Antiviral treatment should be considered for all patients with chronic hepatitis C infection (**AI**). Treatment is recommended for patients at increased risk for development of cirrhosis (i.e., those with chronic hepatitis C who have detectable plasma HCV RNA levels on a qualitative assay, liver biopsy histologic findings of portal or bridging fibrosis and at least moderate inflammation and necrosis, and persistently elevated alanine aminotransferase (ALT) levels >2 times the upper limit of normal) (**BI**). Although patients with normal or only minimally elevated (<2 times the upper limit of normal) ALT levels are likely to have mild disease, some might progress to advanced fibrosis and cirrhosis. Controversy exists about whether to take a biopsy and treat these patients.

Several factors should be considered when making a decision to treat, including genotype, degree of fibrosis, patient motivation, symptoms, severity of other underlying conditions, age, and the need for and the type of concomitant ART. As disease progression is likely to be slow among coinfected patients with mild elevations of ALT and no or minimal fibrosis or inflammatory changes on liver biopsy, these patients might not need treatment and should be monitored periodically with serial determinations of ALT and repeat liver biopsy. The most appropriate intervals to monitor such patients have not been determined.

No data are available to evaluate the safety and effectiveness of antiviral treatment of HCV for HIV-1 coinfected patients with advanced fibrosis or compensated cirrhosis, although some specialists would consider treatment for such patients. Treatment with interferon (IFN)-based therapies is relatively contraindicated among patients with decompensated liver disease, indicated by coagulopathy, encephalopathy, ascites, or history of bleeding varices (**DIII**). Liver transplantation, where feasible, should be the primary treatment option for patients with decompensated liver disease (**CIII**). However, data about the safety and effectiveness of liver transplantation among HIV-1-infected adults are insufficient to recommend its use outside of clinical studies.

The goals of antiviral treatment of chronic hepatitis C include eradication of HCV infection, prevention of histologic progression of hepatic fibrosis and, among persons with HCV-related cirrhosis, prevention of hepatic decompensation, hepatocellular carcinoma, and death. Although the goals of therapy might not be achievable in all patients, histologic and clinical benefits of therapy might not be limited just to persons with clearance of virus. Approved therapies for chronic hepatitis C among HIV-uninfected persons include monotherapy with standard interferons (IFN alfa-2a, alfa-2b, or IFN alfacon-1) or pegylated (PEG) IFNs (alfa-2a and alfa 2b) and combination therapy with standard or PEG IFN alfa 2a or alfa-2b plus ribavirin.

Among HIV-uninfected patients, the combination of PEG IFN plus ribavirin is associated with substantially higher rates of sustained virologic response compared with standard IFNs alone or with ribavirin. Also among HIV-uninfected patients, ribavirin doses adjusted by weight are associated with improved efficacy and less ribavirin-associated toxicity than fixed ribavirin doses. On the basis of ease of administration (once-weekly injection) and the superior efficacy in HIV-

uninfected persons, PEG IFN alfa-2a or -2b plus ribavirin has largely replaced use of standard IFN alfa plus ribavirin for the treatment of chronic hepatitis C infection. Retrospective series and limited, uncontrolled, prospective clinical trials demonstrate that IFN alfa-2b plus ribavirin is reasonably well tolerated and might eradicate HCV infection among certain HIV-1-infected patients. Results from two prospective, randomized, controlled trials comparing PEG IFN alfa-2a plus ribavirin with standard IFN alfa-2a plus ribavirin in HIV-1-infected patients with HCV coinfection demonstrate safety and superior efficacy of PEG IFN alfa-2a plus ribavirin compared with conventional IFN plus ribavirin. Approximately one third of those without a virologic response who underwent liver biopsy had histologic improvement in fibrosis, despite the absence of a virologic response in one trial. On the basis of these data, PEG IFN alfa-2a 180 micrograms administered weekly by subcutaneous injection (or PEG IFN alfa-2b 1.5 micrograms/kg) plus oral ribavirin in a dose of 600 to 1,400 mg daily based on weight is the recommended treatment for chronic hepatitis C among HIV-1-infected persons (**AI**).

Patients with contraindications for the use of ribavirin (e.g., unstable cardiopulmonary disease, preexisting anemia unresponsive to erythropoietin, or hemoglobinopathy) can be treated with PEG IFN alfa (2a or 2b) monotherapy (**AII**). However, decreased rates of sustained virologic response are expected among patients not receiving ribavirin.

The optimal duration of HCV therapy among HIV-1--infected persons is unknown. While awaiting data from ongoing clinical trials, the majority of specialists follow recommendations for HIV-uninfected persons. The duration of treatment using combination therapy with PEG IFN plus ribavirin is 48 weeks for patients with HCV genotype 1 disease who demonstrate an early virologic response (a decrease of at least 2 $\log_{10}$ in HCV viral load as measured by quantitative HCV RNA levels) during the first 12 weeks of treatment (**AI**). Patients with genotype 1 disease who fail to achieve an early virologic response by week 12 have limited chance of achieving a sustained virologic response regardless of duration of therapy, and treatment may be discontinued after 12 weeks in such patients (**BI**). The recommended treatment duration is 24 weeks for HIV-1--infected persons with genotype 2 or 3 disease (**BII**); certain specialists would treat for 48 weeks for coinfected patients with genotype 2 or 3 disease (**CIII**).

Preliminary data among HIV-1-infected patients indicate that the HCV virologic response correlates with pretreatment $CD4^+$ T lymphocyte count (i.e., higher response rates have been observed among patients with baseline $CD4^+$ T lymphocyte counts >500 cells/microliter). Therefore, treatment for HCV should be considered before a decline in $CD4^+$ T lymphocyte count to <500 cells/microliter for patients with HIV-1 coinfection (**BIII**). Conversely, for HIV-1-infected patients with $CD4^+$ T lymphocyte counts <500 cells/microliter, initiation of ART should be considered before treatment for chronic hepatitis C (**BIII**). Clinical trials evaluating this approach are in progress.

Monitoring and Adverse Events

Quantitative HCV RNA levels are the best estimate of treatment response. Reliability and value of serial quantitative measurement as a marker of treatment response remains to be determined, particularly in clinical practice settings where

variation in specimen handling and shipping might decrease validity of HCV RNA change.

A sustained virologic response (SVR) is defined as the absence of detectable HCV RNA, using a qualitative or quantitative HCV RNA assay with a lower limit of detection of 50 IU/mL, at 24 weeks after the end of antiviral treatment. Relapse is defined as the absence of detectable HCV RNA at the end of treatment (ETR) that is not sustained over time. Nonresponse is defined as the absence of an ETR or a SVR. However, even in the absence of a SVR, several studies have demonstrated improved liver histology after completion of a course of antiviral treatment.

HIV-1-infected patients should have a quantitative HCV RNA assay performed at the end of 12 and 24 weeks of treatment, and those with undetectable HCV RNA levels should have an HCV RNA assay repeated 24 weeks after completion of therapy. It is reasonable for coinfected patients who achieve a sustained virologic response to undergo serial HCV RNA testing at 6-month intervals for an additional 1 to 2 years to exclude late virologic relapse (or reinfection with HCV for those at risk for continued exposure).

The major toxicities of IFN alfa (PEG or standard) include influenza-like symptoms (e.g., fever, myalgia, headache, and fatigue), neuropsychiatric abnormalities (e.g., depression and cognitive dysfunction), cytopenias (e.g., thrombocytopenia and neutropenia including a reduction in $CD4^+$ T lymphocyte count), retinopathy, neuropathy, and exacerbation of autoimmune disease. Depression might be severe enough to trigger suicide. Depending on the severity of these toxicities and individual patient tolerance, they might be dose-limiting or interfere with the ability to complete a course of treatment.

The major toxicities of ribavirin include dose-dependent hemolytic anemia, cough, and dyspepsia. In addition, in vitro data have demonstrated drug-drug antagonism between ribavirin and the anti-HIV pyrimidine nucleoside analogues (e.g., zidovudine, stavudine, zalcitabine, and lamivudine). The clinical significance of these drug-drug interactions has not been determined. In addition, ribavirin might potentiate the intracellular activity of didanosine through inhibition of inosine monophosphate dehydrogenase. Case reports have indicated the interaction of RBV and didanosine might lead to clinically significant inhibition of mitochondrial DNA polymerase gamma, resulting in severe pancreatitis and lactic acidosis in certain patients. Until further safety data are available, the combination of ribavirin and didanosine is generally contraindicated (**DIII**).

Complete blood counts, a $CD4^+$ T lymphocyte count, and mental health should be evaluated before initiation of anti-HCV therapy, and the therapy should be monitored at regular intervals during treatment. Adverse effects of IFN alfa and ribavirin might be modified by the use of adjunctive agents such as antidepressants (neuropsychiatric), filgrastim (neutropenia) and erythropoietin (anemia). Although available data are insufficient to recommend the routine use of these agents in the management of HCV, their use should be considered on a case-by-case basis.

Management of Treatment Failure

No recommendations are available for treatment of patients who fail to respond to initial antiviral treatment of chronic hepatitis C. Certain patients might benefit from retreatment with PEG IFN-based regimens depending on their previous response, tolerance, and adherence to and the type of previous therapy (i.e., conventional IFN monotherapy), the potential potency of the new treatment regimen, the severity of liver disease, and viral genotype and other underlying factors that influence response.

Limited data in non-HIV-1-infected persons with HCV indicate that 15 to 20% of nonresponders treated with conventional IFN formulations alone or in combination with ribavirin will achieve a SVR when retreated with PEG IFN and ribavirin. Those who achieved a decline in HCV RNA to levels <100,000 IU/mL during initial treatment with IFN monotherapy or those with genotypes 2 or 3 appear to have better response rates to retreatment. Additional studies evaluating retreatment are in progress.

Prevention of Recurrence

For HIV-1 and HCV coinfected patients, durability of treatment response and the requirement for chronic maintenance therapy to prevent recurrence are unknown. Therefore, no recommendations are available for chronic maintenance therapy in this setting.

Special Considerations During Pregnancy

Pregnant HIV-1-infected women should be tested for HCV infection if not previously tested to allow appropriate management for them and their infants. Transaminase levels tend to decrease and HCV RNA levels to increase during pregnancy. Transaminases might increase transiently postpartum.

Treatment of chronic hepatitis C during pregnancy is not indicated and is not recommended (**DIII**). Both IFN and ribavirin are contraindicated in pregnancy. Although IFNs are not teratogenic among rats, mice, or rabbits, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents. Approximately 30 cases of human exposure to IFNs during pregnancy have been reported, about half in the first trimester, without clear adverse effects.

Ribavirin is labeled as FDA category X because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia. This drug should not be used during pregnancy (**EIII**). Women of child bearing 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. Evaluation, including liver biopsy, can be delayed until $\geq$3 months after delivery to allow potential pregnancy-related changes in disease activity to resolve. Hepatitis A and hepatitis B vaccination can be given during pregnancy.

The risk for perinatal transmission varies from zero among HIV-1-seronegative women with undetectable HCV RNA levels, to 4 to 8% among predominantly HIV-seronegative women with detectable HCV RNA, to 22% among HIV-1-infected women. The risk for perinatal transmission of HCV is consistently higher among

HIV-1-infected compared with HIV-seronegative women, potentially related to higher HCV RNA levels in HIV-1-infected women or concurrent injection drug use. Perinatal transmission of HCV in both HIV-seronegative and HIV-1-infected women also is potentially related to higher HCV RNA levels, although this finding has been inconsistent.

Mother-to-child transmission of HIV-1 also might be more frequent among HCV coinfected women compared with HIV-1-infected women without concomitant HCV infection. Mode of delivery and breast feeding do not appear to influence HCV transmission in HIV-seronegative women, but elective Cesarean delivery might be protective against transmission of HCV among HIV-1-infected women. The adjusted odds ratio for perinatal transmission of HCV with scheduled Cesarean delivery among HIV-1 infected, HCV seropositive women was 0.36 (0.2 to 0.8) compared with other modes of delivery in one large study; however, this study did not control for concomitant perinatal transmission of HIV-1.

Hepatitis B Virus Disease

Treatment Recommendations

All patients with chronic hepatitis B disease should be advised to avoid or limit alcohol consumption because of the effects of alcohol on the liver (**AIII**). In addition, they should be counseled about the risk for household, sexual, and needle-sharing transmission and the need for such contacts to receive hepatitis B vaccine.

Because fulminant hepatic failure from HAV infection occurs at increased frequency among persons with chronic liver disease, persons susceptible to HAV should receive 2 doses of hepatitis A vaccine (**BIII**). HAV vaccine should be administered before the $CD4^+$ T lymphocyte count declines to <200 cells/microliter because the response is likely to be better.

The goals of anti-HBV therapy are to reduce HBV-related morbidity and mortality. Surrogate endpoints include sustained suppression of HBV DNA, prevention of liver disease progression, and clearance of HBeAg; treated patients rarely become HBsAg-negative as HBV reservoirs generally are not sufficiently reduced by available anti-HBV therapy. Limited data indicates that any treatment reduces the risk for HCC.

Antiviral treatment is recommended for patients who have actively replicating virus in blood (as defined by a positive HBeAg or HBV DNA levels $>10^5$ copies/mL) and liver disease as indicated by either an elevated serum ALT (at least 2 times the upper limit of normal) or histopathologic evidence of moderate liver disease activity and/or fibrosis on liver biopsy. The response to therapy is poor for those with a pretreatment ALT level <2 times the upper limit of normal and therapy should generally be deferred for such patients (**DIII**). However, ALT levels fluctuate widely in persons with chronic hepatitis B, and the long-term pattern is more useful than an isolated value in patient management. Certain specialists recommend treatment of those with advanced fibrosis or cirrhosis on liver biopsy with any detectable HBV DNA level provided other causes for chronic liver disease have been eliminated.

No preferred treatment can be uniformly recommended for all HIV-1 coinfected persons with chronic hepatitis B. Therapy should be individualized, taking into account patient-specific considerations. Because of limited data about the safety and efficacy of chronic hepatitis B treatment among HIV-1-infected persons, patients should be encouraged to enroll in clinical trials.

IFN-alfa 2a and 2b, administered in subcutaneous doses of 5 MU daily or 10 MU 3 times per week, are approved for the treatment of chronic hepatitis B disease among HIV-uninfected persons but not among HIV-1-infected patients. Approximately one third of HIV-seronegative patients will clear HBeAg with either of these IFN regimens, and the response is durable among 80 to 90% of persons followed for 4 to 8 years. Among HIV-infected persons with chronic hepatitis B, PEG IFN alfa 2a appears to be superior to standard interferon. If either standard or pegylated interferon is used for treatment among HBeAg-positive patients, 16 to 24 weeks of therapy is recommended (**BII**); for HBeAg negative patients, who respond less well, a minimum of 12 months and possibly longer is recommended (**BIII**). Patients who have a substantial decrease (certain specialists suggest >2 $\log_{10}$ copies/mL) or clearance of HBV DNA in response to IFN-alfa 2a or 2b at week 16 but have persistent HBeAg also might be candidates for longer term treatment of 12 months or longer; however, data are insufficient to make a firm recommendation in HIV-1-infected patients.

Certain specialists recommend that IFN alfa be used in HIV-1 coinfected patients who are candidates for treatment of chronic hepatitis B disease but not HIV-1 (**CIII**). This strategy preserves lamivudine or tenofovir for later treatment of HIV-1 and avoids certain potential complications of ART. IFN-alfa should not be used among patients with decompensated liver disease (**EII**). Studies of PEG IFN-alfa among HIV-uninfected patients with chronic hepatitis B are in progress, and it will probably become the preferred IFN formulation.

For HIV-1-infected persons who are ART-naïve and require ART, lamivudine 150 mg twice daily is commonly used for treatment of chronic hepatitis B, because of its relative safety, anti-HIV activity, wealth of data about its use among HIV-1-infected persons, and the potential toxicity associated with IFN-alfa (**BIII**). Lamivudine should be used together with other antiretroviral drugs in a fully suppressive ART regimen. Because of the high rate of development of HBV resistance to lamivudine monotherapy, certain specialists further recommend the use of lamivudine in combination with either adefovir or tenofovir, although data are limited to support this approach (**CIII**).

Seroconversion of HBeAg (loss of HBeAg, accompanied by development of HBe antibody) occurs in 22% of HBeAg-positive HIV-1-infected patients with chronic hepatitis B who are treated with lamivudine for 1 year. In HIV-seronegative patients, HBeAg seroconversions are sustained among approximately 80% of patients if lamivudine is continued several months after seroconversion. On the basis of limited data on the duration of treatment, HBeAg-positive, HIV-1/HBV coinfected patients who become HBeAg-negative and anti-e-positive on lamivudine therapy should be treated for a minimum of 1 year or at least 6 months beyond HBeAg seroconversion (**BIII**). Among HIV-seronegative, HBeAg-negative patients with chronic hepatitis B who are treated with lamivudine, ALT and HBV DNA levels might decline, but high rates of relapse have been reported when therapy is stopped. Therefore, the optimal duration of treatment of HBeAg-

negative patients, whether HIV-1 infected or not, is unknown (**CIII**). The combination of lamivudine and IFN does not appear to be superior to either medication alone, and is not recommended (**DII**).

Adefovir dipivoxil, 10 mg daily, has no anti-HIV activity and is unlikely to select for HIV-1 resistance; therefore, it is an appropriate alternative to IFN-alfa for coinfected patients who require treatment for chronic hepatitis B but do not yet require ART (**CIII**). However, the long-term safety of adefovir has not been established in HIV-1-infected persons.

Tenofovir, 300 mg daily, has similar in vitro anti-HBV activity to adefovir, and expanding human data indicate it is also active against lamivudine-resistant and wild-type HBV. Although tenofovir is not approved for use in the treatment of HBV infection and data are sparse in HIV-1/HBV coinfected patients, certain specialists consider tenofovir to be the optimal choice for persons who need treatment for both HIV-1 infection and chronic hepatitis B (in conjunction with a fully suppressive ART regimen) (**CIII**). Until long-term data are available that demonstrate the absence of HBV resistance to tenofovir, it might be prudent to use tenofovir in combination with lamivudine (**CIII**). Tenofovir, if used for treatment of HBV in patients receiving ART, should be added as a single agent for this purpose only if plasma HIV-1 RNA levels are undetectable to avoid selection pressure that engenders drug resistance (**CIII**). If therapy is indicated for HIV-1 infection but not for chronic hepatitis B, certain specialists would withhold tenofovir, if possible, to allow for its future use for treatment of chronic hepatitis B (**CIII**).

Emtricitabine (200 mg once daily) is also active against HBV replication and could potentially be substituted for lamivudine; however, data are limited for its use for this indication. It is not active against lamivudine resistant HBV. Famciclovir is less active than lamivudine against HBV and is not active in lamivudine-resistant HBV; therefore, its use is not recommended (**DII**). For HBV treatment-naïve patients who require treatment of both HIV-1 infection and chronic hepatitis B, many specialists would recommend use of an ART regimen that includes either lamivudine or emtricitabine along with either adefovir or tenofovir. However, combination therapy for treatment of HBV in this population is not yet supported by data (**CIII**).

Among patients infected with HBV, HCV, and HIV-1, consideration of the need for ART should be the first priority. If ART is not required, the treatment of HCV should be considered before HBV treatment because IFN therapies for HCV also might treat HBV (**CIII**). If IFN-based therapy for HCV has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs can be considered (**CIII**).

Monitoring and Adverse Events

A virologic response is defined as a substantial (certain specialists recommend >2 $\log_{10}$ copies/mL) decrease in HBV DNA and loss of HBeAg at the end of treatment. A sustained virologic response is defined as suppression of HBV DNA (level not defined) and loss of HBeAg sustained for >6 to 12 months after the end of treatment. Among HIV-uninfected persons, the response rates to IFN-alfa or lamivudine-containing regimens are $\geq$50% in patients with ALT levels >5 times

the upper limit of normal and 20 to 35% among patients with ALT levels between 2 to 5 times the upper limit of normal. Patients for whom therapy is not initiated should be monitored regularly for changes in ALT levels (e.g., every 4 to 6 months).

Other markers of treatment success include improvement in liver histology, normalization of hepatic transaminases, and in those with loss of HBeAg, the development of HBe antibody. Sustained loss of HBsAg is considered by some to be a complete response. Although a decline in HBV viral load correlates with response, no threshold HBV viral load has been established that clearly defines a virological response.

Side effects of IFN-alfa include influenza-like symptoms and fatigue, which can be reduced by premedication with acetaminophen or a nonsteroidal medication. Other common side effects include weight loss, alopecia, thrombocytopenia, anemia, leukopenia (decreased total $CD4^+$ T lymphocyte count but not percentage), depression, and autoimmune disorders. Hypo- or hyperthyroidism, which is often irreversible, might occur 3 to 6 months after initiation of therapy with IFN-alfa. As a result, serum TSH level should be monitored at baseline and periodically (e.g., every 3 months) for the duration of treatment.

Adefovir causes renal tubular disease and renal excretion of carnitine in a substantial proportion of patients at higher doses, but these side effects are uncommon at the 10 mg/day dose. Substantial renal toxicity with tenofovir has not been reported, although isolated cases of increased serum creatinine or renal tubular dysfunction have been observed. Because of the potential for overlapping toxicities and their similar structure, tenofovir and adefovir should not be used in combination.

When anti-HBV therapy with lamivudine, adefovir, or tenofovir is initiated, whether for the purpose of treating chronic hepatitis B or for the treatment of HIV-1 infection, discontinuation is associated with a flare of liver disease in approximately 15% of cases, with loss of the benefit accrued from previous anti-HBV treatment. Certain specialists recommend that when anti-HBV therapies are initiated, they should be continued unless contraindicated or unless the patient has been treated for >6 months beyond loss of HBeAg positivity. However, the risks and benefits of this practice are unknown. If anti-HBV therapy is discontinued and a flare occurs, reinstitution of anti-HBV therapy is appropriate because it can be potentially life saving (**BIII**).

Management of Treatment Failure

The rate of development of lamivudine resistance is approximately 20% per year among HIV-1/HBV coinfected persons treated with lamivudine. Among HIV-1-infected patients who have been on lamivudine and are candidates for treatment of chronic hepatitis B, certain specialists recommend use of adefovir or tenofovir (**CIII**). How long lamivudine should be continued beyond initiation of a new treatment is unknown.

For HIV-1--infected persons previously treated with a lamivudine-containing ART regimen, uncontrolled data indicate that the combination of adefovir with continued lamivudine has substantial antiviral effect even in the presence of

lamivudine-resistant HBV. Certain specialists use adefovir to treat chronic hepatitis B among HIV-1-infected patients who have had an inadequate response to a course of lamivudine therapy as evidenced by high plasma HBV DNA levels or persistent serum HBeAg (**CIII**). Whether lamivudine should be continued (or restarted) if not needed as part of the antiretroviral regimen is unknown.

Although data are sparse and the drug is not approved for this indication, certain specialists would recommend tenofovir to treat chronic hepatitis B among HIV-1-infected patients who require ART and remain HBeAg-positive or have high levels of circulating HBV DNA despite $\geq$12 months of lamivudine (**CIII**). Whether lamivudine should be used (or restarted) in such patients is unknown.

Flares of liver disease have been reported with development of resistance to lamivudine. If this occurs, addition of tenofovir or adefovir might be life-saving (**CIII**). HBV DNA testing might be useful in this setting because increasing levels are associated with emergence of lamivudine resistance or relapse, and stable levels should suggest an alternative cause of acute deterioration.

End-stage liver disease (ESLD) among HBV and HIV-1 coinfected patients is managed as it is in HIV-seronegative patients. IFN is contraindicated in ESLD, but limited data indicate that lamivudine and adefovir (and probably tenofovir) can be safely used. Liver transplantation has been performed with limited success among selected patients with HBV and HIV-1 infection. If a patient is thought to be a candidate for liver transplantation, early consultation with a transplant center should be obtained because transplantation does not cure HBV infection and adequate post-transplant treatment is required (**BIII**).

Prevention of Relapse and Recurrence

Among HIV-seronegative, HBeAg-negative patients with chronic hepatitis B who are treated with lamivudine, ALT, and HBV DNA levels might decline, but high rates of relapse have been reported when therapy is stopped. Therefore, the optimal duration of treatment of HBeAg-negative patients, whether HIV-1 infected or not, is unknown (**CIII**). No known effective means exist to prevent recurrence or flares of chronic hepatitis B.

Special Considerations During Pregnancy

All pregnant women should be screened for HBsAg. 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 for preterm labor and delivery might be increased with acute HBV infection. Treatment of chronic HBV infection is generally not indicated in pregnancy (**DIII**). If antiretrovirals are administered to the mother to prevent HIV transmission, caution should be used in selecting agents like lamivudine or tenofovir that also suppress HBV and may cause hepatitis flare when discontinued. Hepatitis A vaccination, indicated for persons with chronic hepatitis B, can be given during pregnancy.

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and hepatitis B vaccine within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively (**AI**). This

regimen is ≥95% effective in preventing HBV infection in these infants. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9 to 15 months because of the infant's on-going exposure to HBV.

If treatment for chronic hepatitis B disease is necessary, lamivudine is the preferred agent because it is not teratogenic in animals or based on human experience including >1,000 first trimester exposures reported to the Antiretroviral Pregnancy Registry. Lamivudine should only be used in HIV-1-infected pregnant women as part of a fully suppressive ART regimen.

Limited information is available about adefovir. It is embryotoxic in mice and caused neonatal thymic lymphoid tissue destruction with use in later pregnancy in mice. No reports of its use in human pregnancy are available. Cases of exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; email: registry@pharmaresearch.com or http://www.apregistry.com).

Limited information is available about tenofovir. No birth defects have been seen in studies of rats, rabbits, and monkeys. Decreased fetal weights and increased bone porosity were seen in monkeys after high dose exposure in utero. Nineteen cases of first trimester exposure in humans without birth defects have been reported. Cases of exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; email: registry@pharmaresearch.com or www.apregistry.com).

Geographic OIs of Special Consideration

Penicilliosis

Treatment Recommendations

The recommended treatment is amphotericin B in a dose of 0.6 mg/kg body weight/day administered intravenously for 2 weeks, followed by oral itraconazole solution in a dose of 400 mg/day for a subsequent duration of 10 weeks (**AII**). ART should be administered in accordance with standards of care in the community; consideration should be given to simultaneous administration of treatment for penicilliosis and initiation of ART to improve outcome (**CIII**).

Management of Treatment Failure

Alternative treatment options for penicilliosis are not available. For those who fail initial therapy, the approach to treatment should consist of reinitiating parenteral amphotericin B followed by another course of oral itraconazole, coupled with optimizing ART, addressing obstacles to adherence, avoiding adverse drug interactions, and ensuring that adequate absorption and serum concentrations of itraconazole are achieved (**AIII**).

Prevention of Recurrence

Relapse is common in the absence of chronic suppressive therapy. All patients who successfully complete treatment for penicilliosis should be administered

secondary prophylaxis (chronic maintenance therapy) with oral itraconazole in a dose of 200 mg/day (**AI**).

Special Considerations During Pregnancy

Invasive fungal disease should be treated the same in pregnancy as in the nonpregnant adult with the exception that amphotericin B is the preferred agent in the first trimester because of the potential teratogenic effects of azoles.

Leishmaniasis

Treatment Recommendations

Pentavalent antimony, 20 mg/kg body weight/day, administered by intravenous or intramuscular routes, is the initial treatment of choice for leishmaniasis both for cutaneous or visceral disease in many parts of the world (**AII**). The duration of treatment ranges from 3 to 4 weeks depending on the initial response (**CIII**). Antimonials suppress *Leishmania* infection by decreasing the parasite burden in infected macrophages but do not eradicate infection, and relapses commonly follow cessation of therapy among immunosuppressed patients with AIDS. Patients with visceral leishmaniasis might have severe neutropenia and might benefit from a short course of recombinant human (rHu) granulocyte macrophage colony stimulating factor (GM-CSF) 5 micrograms/kg body weight/day administered subcutaneously during the initial 5 days of treatment (**CII**).

Amphotericin B is an effective but less extensively evaluated alternative treatment for leishmaniasis (**AII**). Both the conventional and lipid complex or liposomal encapsulated formulations of amphotericin B appear to have similar efficacy compared with pentavalent antimonials (**AII**). The lipid complex or liposomal preparations are generally better tolerated, and might be preferable to conventional amphotericin B in this setting (**BII**).

The optimal amphotericin B dosage has not been determined. Reported regimens include amphotericin B 0.5 to 1.0 mg/kg body weight/day IV (maximum: 50 mg/day) to achieve a total dose of 1.5 to 2.0 g (**BII**) or lipid complex or liposomal preparations 2 to 5 mg/kg body weight/day over 10 consecutive days (**BII**). If lipid complex or liposomal preparations are used, a higher daily dosage is recommended (**BII**). Pentamidine isethionate, 3 to 4 mg/kg body weight/day administered as a single IV dose infused over at least 60 minutes, at intervals of three times per week for 3 to 4 weeks, is a second-line alternative for treatment of leishmaniasis (**BII**). The following regimens have also been reported to have activity in the treatment of visceral leishmaniasis: allopurinol 20 mg/m^2 in three doses, alone or combined with pentavalent antimony or imidazoles (**CIII**), imidazoles such as ketoconazole (400 to 600 mg/day) or itraconazole (400 mg/day) (**CIII**); and IFN-gamma as adjunctive therapy for severe or refractory cases of visceral leishmaniasis (**CIII**).

Evidence indicates that HIV-1 coinfection alters T helper cytokine responses to *Leishmania*. Poor clinical response to antileishmanial chemotherapy has been reported among coinfected patients who have high plasma HIV-1 RNA levels. Data further indicate that patients receiving ART who present with visceral leishmaniasis have better outcomes than those not receiving ART. As such, strong

consideration should be given to initiation or optimization of ART among patients who present with leishmaniasis (**CIII**).

Monitoring and Adverse Events

Patients receiving pentavalent antimonials should be monitored closely for adverse reactions, which are frequent and vary from mild phlebitis to death. Overall, at a dose of 20 mg/kg bodyweight/day, $\geq$60% of patients might have one or more of the following reactions: local pain at the site of injection, thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and in some patients, clinical pancreatitis. Occasional electrocardiographic changes might be observed (e.g., prolonged QT intervals and T wave inversion). Rarely, arrhythmias and sudden death have occurred.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions, which might be ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids (**CIII**). Previous fluid expansion with colloidal fluids might help reduce the risk for nephrotoxicity during treatment (**CIII**).

Management of 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 use of one or more of the recommended alternatives for initial therapy as outlined above should be considered (**CIII**). The response rate for retreatment appears to be similar to that for initial therapy although certain patients might evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies (**CIII**).

Although data to support its use among HIV-1-infected persons are limited, miltefosine might be an alternative oral agent for use as salvage therapy in countries outside the United States (**CIII**). The drug is approved and available in India and registration in Europe is pending. The adult dose is 100 mg daily for 4 weeks. Cure rates in HIV-seronegative patients are reported at approximately 95%. A phase II trial from India indicated that miltefosine was as effective as amphotericin B for the treatment of visceral leishmaniasis in HIV-seronegative patients. Gastrointestinal side effects are the most common adverse effects but rarely limit treatment.

Prevention of Recurrence

Among patients with visceral leishmaniasis who are not receiving or responding to ART, the risk for relapse at 6 and 12 months, in the absence of secondary prophylaxis (chronic maintenance therapy), is 60% and 90%, respectively. Therefore, secondary prophylaxis with pentavalent antimony, amphotericin B, or pentamidine, administered at least every 2 to 4 weeks, is recommended, particularly for those with $CD4^+$ T lymphocyte counts <200 cell/microliter (**AII**).

Relapse after discontinuation of secondary prophylaxis or maintenance therapy for leishmaniasis is uncommon among patients who respond to ART and maintain a $CD4^+$ T-lymphocyte count >200 cells/microliter, although relapse might be more common among those with visceral leishmaniasis, even with $CD4^+$ T lymphocyte counts >200 cells/microliter and undetectable plasma HIV-1 RNA. Although data are insufficient to provide a recommendation, discontinuation of secondary prophylaxis after successful treatment of leishmaniasis might be considered after a sustained (i.e., $\geq$3 to 6 months) increase in the $CD4^+$ lymphocyte count to levels >350 cells/microliter after initiation of ART (**CIII**). Daily allopurinol, in a dose of 300 mg three times daily, used for maintenance therapy is less effective than monthly pentavalent antimony and is not recommended (**DIII**).

Special Considerations During Pregnancy

Diagnostic considerations are the same among pregnant women as in nonpregnant adults. Labeling for pentavalent antimony compounds (sodium stibogluconate available in the United States through CDC and meglumine antimoniate) states that they are contraindicated among pregnant women, although various compounds were not teratogenic among chickens, rats, or sheep. A single case report of use of meglumine antimoniate in the second trimester of human pregnancy reported a good outcome for mother and infant. Because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy, amphotericin B would be the first choice for therapy of visceral leishmaniasis in pregnancy if the *Leishmania* species causing infection is expected to be responsive to amphotericin B (**AIII**). Pentamidine would be the second choice, and antimony compounds reserved for infections not responsive to the other two agents (**AIII**).

Perinatal transmission of *Leishmania* spp. occurs rarely; eight documented cases have been reported. No data on the risk for transmission of *Leishmania* spp. among HIV-1-infected pregnant women are available.

Paracoccidioidomycosis

Treatment Recommendations

No published randomized clinical trials for the treatment of paracoccidioidomycosis exist. The majority of specialists recommend amphotericin B for initial therapy in severe cases (**BII**), but the efficacy of other agents (e.g., TMP-SMX and azole antifungals) might be comparable. In particular, single-arm studies of itraconazole, 100 to 200 mg daily, ketoconazole 200 to 400 mg, and sulfonamides have demonstrated activity in immunocompetent hosts (**BII**). Fluconazole is associated with a higher failure rate even at doses up to 600 mg daily and is not recommended. Potent ART should be administered in accordance with standards of care in the community (**AIII**).

Management of Treatment Failure

In the absence of any clinical trials to indicate approaches to the treatment of patients who fail to respond or who relapse after initial treatment, consideration should be given to retreatment with amphotericin B or to the use of azole antifungals (**CIII**).

Prevention of Recurrence

Secondary prophylaxis (i.e., chronic maintenance therapy) to prevent relapse should be considered for patients with AIDS and $CD4^+$ T lymphocyte counts of <200 cells/microliter, although no data indicate appropriate regimens in this setting. ART should be optimized.

Special Considerations During Pregnancy

Invasive fungal infections should be treated the same in pregnancy as among the nonpregnant woman. Amphotericin B is the preferred agent in the first trimester because of the potential teratogenic risks for the azoles, if efficacy of amphotericin is expected to be similar to that of azoles (**BIII**).

Isosporiasis

Treatment Recommendations

Fluid support should be offered if the diarrhea has resulted in dehydration (**AIII**). Malnutrition and wasting should be treated with nutritional supplementation (**AIII**). The drug of choice for therapy is trimethoprim (160 mg) and sulfamethoxazole (800 mg) administered four times a day for 10 days (**AII**). Doses of oral trimethoprim (320 mg) plus sulfamethoxazole (1,600 mg) taken twice a day for 10 to 14 days is as effective and might be associated with improved adherence and tolerability (**AIII**). Treatment with TMP-SMX results in clearance of parasites, decreased volume of diarrhea, and decreased abdominal pain within a mean of 2.5 days after initiation of treatment.

No effective alternative treatment is available for patients unable to tolerate sulfonamides. Several agents have been used with anecdotal success. Pyrimethamine used alone in doses of 50 to 75 mg/day appears comparable to treatment with trimethoprim and sulfamethoxazole (**BII**). When pyrimethamine is used, it should be administered with folinic acid (5 to 10 mg/day) to prevent bone marrow suppression (**BII**). Ciprofloxacin and other fluoroquinolones have demonstrated activity against other *Apicomplexa* in animal studies and might be second-line alternatives for treatment of isosporiasis (**BII**). In a limited, randomized clinical trial comparing ciprofloxacin with TMP-SMX among HIV-1-infected patients with isosporiasis, all patients treated with TMP-SMX cleared the organism and had cessation of diarrhea within a median of 2 days; ciprofloxacin was effective in 83% of patients with a median time to cessation of diarrhea of 4.5 days.

Treatment with other anti-protozoal agents (e.g., metronidazole, tinidazole, quinacrine, and furazolidone) is probably of limited value and is not recommended (**DIII**). Immune restoration after ART among patients with AIDS is associated with more rapid resolution of symptoms and fewer relapses. Therefore, ART is recommended as part of the treatment for patients with isosporiasis (**AIII**).

Management of Treatment Failure

Treatment failure is defined as persistence or worsening of diarrhea and systemic symptoms after 5 to 7 days of appropriate treatment. Retreatment with a second-line alternative agent might result in improvement in those who fail initial therapy (**BIII**).

Macrolide antibiotics have marginal efficacy in treating *Isospora belli* enteritis (**CII**). Spiramycin (1.5 g twice daily) and roxithromycin (2.5 mg/kg body weight every 12 hours) have been effective in a limited number of patients with AIDS and chronic refractory isosporiasis. Diclazuril (200 to 300 mg/day for 7 days), nitazoxanide (500 mg twice a day for 7 to 10 days), and albendazole coupled with ornidazole were effective in limited numbers of patients with AIDS and *I. belli* diarrhea and might be tried among patients unresponsive to (or intolerant of) TMP-SMX (**CII**).

Prevention of Recurrence

Infections tend to be chronic and relapsing, particularly in patients with AIDS and advanced immunosuppression. Treatment is usually effective in controlling symptoms, but recurrences are common after treatment is stopped, probably because the agents used to treat the infection are not active against the extraintestinal tissue cyst stage of the parasite.

Patients with $CD4^+$ T lymphocyte counts <200 cells/microliter should receive secondary prophylaxis (chronic maintenance therapy) with trimethoprim (320 mg) and sulfamethoxazole (1,600 mg) once daily or three times a week (**AII**). Pyrimethamine, 25 mg per day, also has been used successfully for secondary prophylaxis following primary isosporiasis (**BII**).

Although not evaluated in any clinical trial or observational cohort setting, it is likely, as with other similar opportunistic infections, that secondary prophylaxis can be safely discontinued after an increase in $CD4^+$ T lymphocyte counts to levels >200 cells/microliter sustained for at least 3 to 6 months following initiation of ART (**BIII**).

Special Considerations During Pregnancy

The incidence, clinical manifestations, and course of *I. belli* infection do not appear to differ with pregnancy. Diagnosis and therapy should be the same as among nonpregnant women.

Chagas Disease

Treatment Recommendations

Treatment for Chagas disease is uniformly effective among patients with chronic stage disease; however, the available agents are toxic, and consultation with a specialist should be sought. Benznidazole, 5 to 8 mg/kg body weight/day for 30 to 60 days, is the initial treatment most commonly recommended (**AIII**). Nifurtimox, 10mg/kg body weight/day, is an alternative (**BIII**). Limited data are available evaluating the efficacy of these agents among HIV-1-infected patients with Chagas disease. Neither drug is licensed in the United States; however,

nifurtimox is available from CDC under an investigational protocol. Although no data are available specifically to address this question, treatment of acute Chagas disease is likely to be more effective than treatment of patients with late-stage complications.

The potential impact of immune reconstitution caused by ART on HIV-1-related Chagas disease remains to be established; however, it seems likely that maintaining normal immune function will decrease the frequency of reactivation of *Trypanosoma cruzi*, as it has with other OIs. As such, initiation or optimization of ART should be considered for patients undergoing treatment for Chagas disease, but information is limited about drug interactions between agents used to treat Chagas disease and available antiretroviral agents (**CIII**).

Monitoring and Adverse Effects

Patients undergoing treatment should be closely monitored because both benznidazole and nifurtimox are toxic. Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, seizures, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

Management of Treatment Failure

Although no data are available among HIV-1-infected persons, certain specialists recommend retreatment with benznidazole or nifurtimox for patients who fail to respond or relapse following initial therapy (**CIII**).

Prevention of Recurrence

Patients with HIV-1-infection are potentially at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection. The drugs are only partially effective in the chronic stage of disease, are suppressive rather than curative, and probably require lifelong administration to prevent relapse in the setting of continued immunosuppression. Precise doses and regimens have not been described (**CIII**). Whether secondary prophylaxis or chronic maintenance therapy should be used routinely among HIV-1-infected patients with latent Chagas disease is unclear. Whether chronic maintenance therapy can be safely discontinued for persons on ART who have a sustained increase in $CD4^+$ T lymphocyte count to levels >200 cells/microliter is uncertain.

Special Considerations During Pregnancy

The seroprevalence of *T. cruzi* infection among pregnant women in areas where the disease is endemic in Latin America ranges from as high as 50% in urban areas to 81% in rural areas. In the United States, seroprevalence data are limited, but one 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. No data are available on the prevalence of *T. cruzi* antibodies among HIV-1-infected pregnant women in the United States.

Congenital infection with *T. cruzi* might increase the risk for spontaneous abortion, stillbirth, and low birthweight. Congenital Chagas disease in newborn infants ranges from subclinical to life-threatening with severe neurological and cardiac disease. No data are available to evaluate whether the combination of HIV-1 infection and *T. cruzi* infection increases the risk for adverse pregnancy outcomes. Diagnosis is the same in pregnancy as among nonpregnant adults.

Both benznidazole and nifurtimox are associated with substantial toxicity in chronic *T. cruzi* infection. Minimal data are available on potential reproductive toxicity of these drugs, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease. Benznidazole crosses the placenta in rats and covalently binds to fetal proteins. Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection among pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered after completion of the pregnancy. For HIV-1-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, maximization of the immune response with ART should be the primary approach to therapy (**AIII**).

Perinatal transmission of *T. cruzi* might occur with acute infection during pregnancy, which has been described rarely, or more often, with reactivation of chronic infection. Perinatal transmission rates among general populations of pregnant women seropositive for antibodies to *T. cruzi* range from 2 to 10%.

The effect of concurrent HIV-1 infection in the mother on risk for perinatal transmission of *T. cruzi* is not well defined, but the risk for reactivation and transmission might be increased among women with advanced immunosuppression. Infants coinfected with HIV-1 and *T. cruzi* might be more likely to have symptoms, especially neurologic symptoms.

Definitions

Strength of the Recommendation

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered**.
B. Moderate evidence for efficacy – or strong evidence for efficacy but only limited clinical benefit – support recommendation for use. **Should generally be offered**.
C. Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. **Optional**.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered**.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered**.

Quality of Evidence Supporting the Recommendation

I: Evidence from at least one properly designed randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment of opportunistic infections in human immunodeficiency virus (HIV)-infected adults and adolescents

POTENTIAL HARMS

Adverse Effects and Drug Interaction

- Major toxicities and interactions of the drug preparations used in treatment of opportunistic infections are discussed in the "Major Recommendations" section of this summary.
- In addition, tables in the original guideline document provide information on common toxicities of systematic agents for treatment of opportunistic infections (Table 7), drug interactions of clinical significance (Table 8), and antiretroviral anti-infective drug combinations that should be avoided (Table 9).

CONTRAINDICATIONS

CONTRAINDICATIONS

- Once-weekly rifapentine is contraindicated among human immunodeficiency virus (HIV)-1–infected patients, and it is recommended that rifampin (RIF)- and rifabutin-based regimens be given at least three times a week for patients with tuberculosis (TB) and advanced HIV-1 disease (CD4+ T lymphocyte count <100 cells/microliter) supplemented by ethambutol (EMB) for the first 2 months, thereby avoiding pyrazinamide (PZA).

- For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected.
- Treatment with interferon (IFN)-based therapies is relatively contraindicated among patients with decompensated liver disease, indicated by coagulopathy, encephalopathy, ascites, or history of bleeding varices.
- Contraindications for the use of ribavirin include unstable cardiopulmonary disease, preexisting anemia unresponsive to erythropoietin, and hemoglobinopathy.
- Both IFN and ribavirin are contraindicated in pregnancy.
- IFN is contraindicated in end-stage liver disease (ESLD).
- Labeling for pentavalent antimony compounds (sodium stibogluconate available in the United States through CDC and meglumine antimoniate) states that they are contraindicated among pregnant women, although various compounds were not teratogenic among chickens, rats, or sheep.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This report does not include any discussion of a product under investigational use. However, this report does contain discussion of certain drugs indicated for use in a nonlabeled manner and that are not Food and Drug Administration (FDA) approved for such use. Each drug used in a nonlabeled manner is identified in the text. Information included in these guidelines might not represent FDA approval or approved labeling for the particular products or indications being discussed. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.
- These guidelines are written for physicians and other health-care providers who care for human immunodeficiency virus (HIV)-1-infected persons in the United States and Western Europe where access is available to a full range of up-to-date medical services; however, these recommended strategies might not be feasible or appropriate in all settings where the spectrum of HIV-1-related complications and diagnostic capacity differ from those observed in the United States and Western Europe.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 17;53(RR-15):1-118. [693 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

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GUIDELINE COMMITTEE

CDC-National Institutes of Health (NIH)-Infectious Diseases Society of America (IDSA) Guidelines for the Treatment of Opportunistic Infections in Adults and Adolescents Infected with Human Immunodeficiency Virus Panel

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Centers for Disease Control and Prevention (CDC), the guideline planners, and content specialists have disclosed that they have no financial interests or other relationships with the manufactures of commercial products, suppliers of commercial services, or commercial supporters.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Treating opportunistic infections among HIV-infected adults and adolescents. Continuing education credit. MMWR Morb Mortal Wkly Rep 2004 Dec 17;RR-15

Electronic copies: Available in Portable Document Format (PDF) from the Centers for Disease Control and Prevention (CDC) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 23, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was most recently updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on February 21, 2006 following the U.S. Food and Drug Administration (FDA) advisory on Tequin (gatifloxacin). This summary was updated by ECRI on March 3, 2006 following the FDA advisory on varicella zoster immune globulin (VZIG). This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium). This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on February 26, 2008 following the U.S. Food and Drug Administration advisory/voluntary market withdrawal of the liquid formulation of Leukine (sargramostim). This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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