Complete Summary

GUIDELINE TITLE

Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references] PubMed

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 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.
- 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

SCOPE

DISEASE/CONDITION(S)

Opportunistic infections among human immunodeficiency virus (HIV)-exposed and -infected children including:

- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Toxoplasmosis
- Cryptosporidiosis/Microsporidiosis
- Mycobacterium tuberculosis (TB)
- *Mycobacterium avium* complex (MAC) disease
- Serious and recurrent bacterial infections including pneumonia, bacteremia, urinary tract infection, osteomyelitis, meningitis, abscess, and septic arthritis
- Syphilis
- *Candida* infections (Oropharyngeal Candidiasis [OPC], esophageal disease, and invasive diseases)
- Cryptococcosis
- Histoplasmosis
- Coccidioidomyocosis
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV) infection
- Varicella-Zoster virus (VZV) infection
- Human Papillomavirus (HPV) infection
- Hepatitis C
- Hepatitis B

GUIDELINE CATEGORY

Diagnosis
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 infants, children, and adolescents in the United States
- To serve as a companion to the United States Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) *Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Persons* and the *Guidelines for the Treatment of Opportunistic Infections in Persons Infected with the Human Immunodeficiency Virus, which is focus on HIV-infected adults*

TARGET POPULATION

Human immunodeficiency virus (HIV)-exposed or infected infants, children, and adolescents with opportunistic infections living in the United States

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Physical examination
2. Induced sputum analysis
3. Bronchoscopy with bronchoalveolar lavage
4. Fiberoptic bronchoscopy with transbronchial biopsy
5. Open-lung biopsy
6. Enzyme-linked immunoassay (EIA)
7. Immunosorbent assay
8. Immunofluorescence
9. Recombinant immunoblot assay
10. Isolation of parasite by mouse inoculation, or inoculation in tissue cultures
11. Deoxyribonucleic acid (DNA) detection using polymerase chain reaction (PCR)
12. Serologic testing
13. DNA, ribonucleic acid (RNA), or organism isolation from white blood cells, cerebrospinal fluid (CSF), amniotic fluid, tissues, gastric aspirate samples, sputum, or pleural fluid
14. Measurement of IgG, IgM, IgA, or IgE antibodies
15. Stool sample
16. Urine sediment examination
17. Endoscopy
18. Tuberculin skin tests
19. Radiography
20. Antibiotic susceptibility testing
21. Antibody titers
22. Antigen titers

23. Complete blood count
24. Differential and platelet count
25. Viral load
26. Monitoring for drug toxicity:
    - Serum transaminases
    - Thyroid-stimulating hormone (TSH) levels

Management/Treatment

1. Trimethoprim/sulfamethoxazole (TMP/SMX) (Bactrim, Septra)
2. Pentamidine isethionate (Pentam®)
3. Trimethoprim/sulfamethoxazole + pentamidine isethionate (considered, but not recommended)
4. Atovaquone (Mepron®)
5. Clindamycin (Cleocin®)
6. Primaquine
7. Trimetrexate glucuronate with leucovorin (folinic acid)
8. Dapsone/trimethoprim
9. Corticosteroids (including prednisone, methylprednisolone, or dexamethasone)
10. Pyrimethamine [Daraprim®]/sulfadiazine/leucovorin (folinic acid)
11. Spiramycin
12. Azithromycin/pyrimethamine/leucovorin
13. Atovaquone/pyrimethamine/leucovorin
14. Atovaquone/leucovorin
15. Azithromycin (Zithromax®)
16. Nitazoxanide (Alinia®)
17. Paromomycin (Humatin®)
18. Oral hyperimmune bovine colostrums
19. Oral immune globulin
20. Albendazole (Albenza®)
21. Fumagillin
22. Isoniazid
23. Rifampin (Rifadin®)
24. Pyrazinamide
25. Ethambutol (Myambutol®)
26. Ethionamide (Trecator-SC®)
27. Streptomycin
28. Rifabutin (Mycobutin®)
29. Kanamycin
30. Amikacin
31. Capreomycin (Capastat®)
32. Quinolones (ciprofloxacin [Cipro®], ofloxacin, levofloxacin, and moxifloxacin)
33. Cycloserine (Seromycin®)
34. Para-amino salicylic acid
35. Clarithromycin (Biaxin®)
36. Clofazimine (not recommended)
37. Extended-spectrum cephalosporins (ceftriaxone, cefotaxime, or cefuroxime)
38. Ceftazidime
39. Vancomycin
40. Haemophillus influenzae type B (Hib) and heptavalent pneumococcal conjugate vaccines

41. Erythromycin
42. Aqueous crystalline penicillin G
43. Procaine penicillin G
44. Benzathine penicillin G
45. Clotrimazole troches
46. Nystatin suspension
47. Amphotericin B (conventional and lipid complex formulations) (Fungizone®, Abelcet®, Ambisome®)
48. Azoles (fluconazole [Diflucan®], ketoconazole [Nizoral®] itraconazole [Sporanox®], or voriconazole [VFEND®])
49. Caspofungin (Cancidas®)
50. Flucytosine (Ancoban)
51. Surgical debridement
52. Ganciclovir (Cytovene®)
53. Foscarnet (Foscarvir®)
54. Valganciclovir (Valcyte®)
55. Cidofovir (Vistide®)
56. Fomivirsen (Vitravene)
57. Acyclovir (Zovirax®)
58. Valacyclovir (Valtrex®)
59. Penciclovir
60. Famciclovir
61. Cryotherapy
62. Electrodesiccation
63. Podofilox solution and gel
64. Imiquimod cream
65. Trichloroacetic or bichloroacetic acid aqueous solution
66. Podophyllin resin
67. Acid cauterization
68. Cidofovir
69. Hepatitis A vaccine
70. Pegylated interferon-alfa (Interferon-alfa-2a or -2b)
71. Lamivudine (3TC) (Epivir®)
72. Adefovir
73. Tenofovir
74. Ribavirin

MAJOR OUTCOMES CONSIDERED

- Predictive value of diagnostic tests
- CD4+ cell count
- Mortality
- Survival
- Sensitivity and specificity of diagnostic tests
- Signs and symptoms
- Control of opportunistic infections
- Recurrence of infection
- Toxicities, drug interactions, and the potential to induce drug resistance

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

During development of these guidelines, members of the pediatric treatment guidelines writing group and of the Working Group on Antiretroviral Therapy and Management of Human Immunodeficiency Virus (HIV)-Infected Children reviewed published manuscripts and abstracts presented at professional meetings related to treatment of selected pathogens among children and adults.

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 Recommendations

I: Evidence from at least one 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

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In 2001, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health, and the Infectious Diseases Society of America convened a

working group to develop guidelines for therapy of human immunodeficiency virus (HIV)-associated opportunistic infections to serve as a companion to the Guidelines for Prevention of Opportunistic Infections Among HIV-Infected Persons. In recognition of unique considerations related to HIV infection among infants, children, and adolescents, a separate pediatric working group was established.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of the Recommendation

Rating: A

Strength of recommendation: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use.

Should always be offered.

Rating: B

Strength of recommendation: Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use.

Should generally be offered.

Rating: C

Strength of recommendation: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g. drug toxicity, drug interactions) or cost of the treatment or alternative approaches.

Optional.

Rating: D

Strength of recommendation: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Should generally not be offered.

Rating: E

Strength of recommendation: 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 made available for public comment through announcements published in the *Federal Register* and the *Morbidity and Mortality Weekly Report (MMWR)*.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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 Appendix A of the original guideline document for a summary of recommendations for treatment of opportunistic infections among human immunodeficiency virus (HIV)-exposed and -infected infants; to Appendix B for information on preparations and major toxicities of common drugs used for treatment of opportunistic infections in HIV-infected children; and to Appendix C for information on drug interactions of clinical significance.

Pneumocystis jiroveci **(formerly *carinii*) Pneumonia (PCP)**

Trimethoprim/sulfamethoxazole (TMP/SMX) is the recommended treatment for PCP (**AI**). The dose for HIV-infected children aged >2 months is 15-20 mg/kg body weight/day of the TMP component (75-100 mg/kg of SMX component) administered intravenously in 3-4 divided doses, with the dose infused over 1 hour for 21 days (**AI**). After the acute pneumonitis has resolved, children with mild to moderate disease who do not have malabsorption or diarrhea can be administered oral treatment with the same dose of TMP/SMX in 3-4 divided doses to complete a 21-day course.

Adverse reactions to TMP/SMX reported in children include rash (including erythema multiforme and rarely Stevens Johnson syndrome), hematologic abnormalities (e.g., neutropenia, thrombocytopenia, megaloblastic, or aplastic anemia), gastrointestinal complaints (usually mild), hepatitis, and renal disorders (e.g., interstitial nephritis). The overall frequency of adverse reactions appears to be lower among HIV-infected children than adults; approximately 15% of children have substantial adverse reactions to TMP/SMX. For mild or moderate skin rash, TMP/SMX can be temporarily discontinued and restarted when the rash has

resolved. If an urticarial rash of Stevens-Johnson syndrome occurs, TMP/SMX should be discontinued and not readministered (**EIII**).

Pentamidine isethionate (4 mg/kg/day once daily administered intravenously over 60-90 minutes) is recommended for patients intolerant of TMP/SMX or who demonstrate clinical treatment failure after 5-7 days of TMP/SMX therapy (**AI**). No evidence exists for synergistic or additive effects on efficacy of these agents; therefore, because of potential increased toxicity; their combined use is not recommended (**DIII**). Among patients with clinical improvement after 7-10 days of intravenous therapy with pentamidine, an oral regimen (e.g. atovaquone) might be considered to complete a 21-day course (**BIII**).

The most common adverse drug reaction to pentamidine is renal toxicity, which usually occurs after 2 weeks of therapy and can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval (torsades de pointes), and cardiac arrhythmias can occur. Hypoglycemia (usually after 5-7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus have also been reported. A metallic or bitter taste might be experienced. Serious adverse reactions to pentamidine have been reported in approximately 17% of children receiving pentamidine. Care should be taken if administering this drug with other nephrotoxic agents (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) or if coadministered with agents associated with pancreatitis (e.g., didanosine).

Atovaquone is an alternative for treatment of mild to moderately severe PCP in adults (**BI**). Data are limited for children; dosage is 30-40 mg/kg/day in 2 divided doses given orally with fatty foods. Food increases the bioavailability of atovaquone 1.4-fold over that achieved with the fasting state. Infants aged 3-24 months might require a higher dosage of 45 mg/kg/day (**AII**). Atovaquone concentration is increased with coadministration of fluconazole and prednisone and decreased by coadministration with acyclovir, opiates, cephalosporins, rifampin, and benzodiazepines. Most adverse reactions occur after the first week of therapy. Skin rashes (10-15%), nausea, and diarrhea can occur. Elevated liver enzymes also might be observed.

Clindamycin/primaquine has been used for treatment of mild to moderate PCP among adults (**BI**); data for children are not available (**CIII**). Primaquine is contraindicated among patients with glucose-6-dehydrogenase deficiency associated with the possibility of inducing hemolytic anemia. Dose information for treatment of PCP is available only for adults. For patients weighing <60 kg, clindamycin 600 mg intravenously every 6 hours for 10 days, then 300-450 mg orally every 6 hours to complete 21 days of treatment is recommended. Primaquine is administered as 30 mg of the base orally for 21 days. Dosing for children is based on use of these drugs for treatment of other infections: the usual pediatric dose of clindamycin for treatment of bacterial infections is 10 mg/kg every 6 hours, and the pediatric dose of primaquine equivalent to an adult dose of 30 mg base (when used for malaria) is 0.3 mg/kg of the base daily. Adverse reactions include skin rashes, nausea, and diarrhea.

Trimetrexate glucuronate with leucovorin (folinic acid) has been used as initial therapy in severe PCP in adults (**BI**); data are limited for children (**CIII**). The

dose is 45 mg/m^2/day of trimetrexate glucuronate for 21 days. Leucovorin should be administered at 20 mg/m^2 every 6 hours for 24 days.

Dapsone/trimethoprim is effective in treatment of mild-to-moderate PCP among adults (**BI**); data on toxicity and efficacy among children are not available (**CIII**). The dose for adults of dapsone is 100 mg orally once daily and trimethoprim 15 mg/kg divided into 3 daily doses orally, administered for 21 days. Among children aged <13 years, a dapsone dose of 2 mg/kg/day is required to achieve therapeutic levels in children (**AII**). The pediatric dose of trimethoprim is 15 mg/kg divided into 3 daily doses. The primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, anemia, and thrombocytopenia.

On the basis of studies in adults, a short course of corticosteroids might be indicated in some cases of PCP of moderate or great severity, started within 72 hours of diagnosis (**AI**). Pediatric studies have indicated reduction in acute respiratory failure, decreased need for ventilation, and decrease in mortality with early use of corticosteroids in HIV-infected children with PCP. Indications for corticosteroid treatment include a PaO_2 value of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. Doses in children varied between studies. Alternative regimens include 1) prednisone on days 1-5, 40 mg twice daily; days 6-10, 40 mg once daily; days 11-21, 20 mg once daily; 2) prednisone (or methylprednisolone sodium) on days 1-5, 1 mg/kg twice daily; day 6-10, 0.5 mg/kg twice daily; days 11-21, 0.5 mg/kg once daily; or 3) methylprednisolone (intravenous) on days 1-7, 1 mg/kg every 6 hours; days 8-9, 1 mg/kg twice daily; days 10-11, 0.5 mg/kg twice daily; days 12-16, 1 mg/kg once daily.

Some case reports about children have documented improved pulmonary function with use of surfactant in cases of severe disease (e.g., respiratory distress syndrome with established respiratory failure requiring ventilation)(**CIII**).

Among HIV-infected children, lifelong suppression is indicated following treatment for PCP to prevent recurrence; details on secondary prophylaxis (maintenance therapy) have been published. Safety of discontinuation of secondary prophylaxis after immune reconstitution with highly active antiretroviral therapy (HAART) in children has not been studied extensively.

Toxoplasmosis

Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital *Toxoplasmosis* should be managed in consultation with an appropriate specialist. If an HIV-infected woman has a symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered whether or not the mother was treated during pregnancy (**BIII**).

The preferred treatment for congenital toxoplasmosis is pyrimethamine (loading dose of 2 mg/kg body weight/day for 2 days, then 1 mg/kg/day for 2-6 months, followed by 1 mg/kg administered three times a week) combined with sulfadiazine (50 mg/kg/dose twice daily), with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity (**AII**). Although the optimal duration of therapy is undefined, the recommended duration of treatment

of congenital toxoplasmosis for infants without HIV infection is 12 months (**AII**). Absent definitive data, the same recommendation applies to HIV-infected children with congenital toxoplasmosis.

For children without HIV infection who have mild congenital toxoplasmosis, certain experts alternate pyrimethamine/sulfadiazine/folinic acid monthly with spiramycin (50 mg/kg orally twice daily) from the seventh through the 12th month of treatment (**CIII**). However, among children with moderate to severe disease and those with HIV infection, the full 12-month regimen of pyrimethamine/ sulfadiazine should be administered (**AII**).

HIV-infected children with acquired central nervous system (CNS), ocular, or systemic toxoplasmosis should be treated with pyrimethamine (2 mg/kg/day for 3 days, followed by 1 mg/kg/day) and leucovorin (1025 mg/day) plus sulfadiazine (25-50 mg/kg/dose given four times daily) **(AI)**. Acute therapy should be continued for 6 weeks, assuming clinical and radiological improvement (**BII**). Longer courses of treatment might be required in cases of extensive disease or poor response after 6 weeks.

Pyrimethamine can be associated with rash (including Stevens-Johnson syndrome) and nausea. The primary toxicity of pyrimethamine is reversible bone marrow suppression (i.e., neutropenia, anemia, and thrombocytopenia). A complete blood count should be performed at least weekly while the child is on daily pyrimethamine and at least monthly while on less than daily dosing (**AIII**). Leucovorin (folinic acid) should always be administered with pyrimethamine; increased doses of leucovorin might be required in the event of marrow suppression. Because of the long half-life of pyrimethamine, leucovorin should be continued 1 week after pyrimethamine has been discontinued.

Adverse effects of sulfadiazine include rash, fever, leucopenia, hepatitis, gastrointestinal symptoms (nausea, vomiting, and diarrhea), and crystalluria. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin (5.0-7.5 mg/kg orally 4 times daily; maximum 600 mg/dose), administered with pyrimethamine and leucovorin (**AI**). Clindamycin can be associated with fever, rash, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, including pseudomembranous colitis) and hepatotoxicity.

Azithromycin (900-1,200 mg/day) also has been used with pyrimethamine and leucovorin among sulfa-allergic adults instead of clindamycin (**BII**), but this regimen has not been studied among children (**CIII**). Another alternative in adults is atovaquone (1,500 mg orally twice daily, administered with meals) plus pyrimethamine and leucovorin, or atovaquone with sulfadiazine alone, or atovaquone as a single agent among patients intolerant to both pyrimethamine and sulfadiazine (**BII**); however, these regimens have not been studied among children (**CIII**). Trimethoprim-sulfamethoxazole (5 mg/kg trimethoprim plus 25 mg/kg sulfamethoxazole intravenously or orally administered twice daily) alone has been used as an alternative to pyrimethamine-sulfadiazine among adults (**BI**), but this has not been studied among children (**CIII**).

Corticosteroids (e.g., dexamethasone or prednisone) have been used among children with CNS disease when cerebrospinal fluid (CSF) protein is very elevated (i.e., >1,000 mg/dL) or with focal lesions with substantial mass effects (**BIII**).

Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible. Among HIV-infected children, lifelong suppression is indicated after treatment for toxoplasmosis to prevent recurrence; details on secondary prophylaxis (i.e., maintenance therapy) have been published. Safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied extensively.

Cryptosporidiosis/Microsporidiosis

Immune reconstitution resulting from HAART frequently results in clearance of *Cryptosporidium* and *Microsporidium* infections. Effective HAART is the recommended treatment for these infections (**AII**). Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (**AIII**). Antimotility agents should be used with caution among young children (**CIII**).

No consistently effective therapy is available for either cryptosporidiosis or microsporidiosis, and duration of treatment among HIV-infected persons is uncertain. Certain agents have demonstrated efficacy in decreasing the severity of symptoms among children. Nitazoxanide is approved for treatment of diarrhea caused by *Cryptosporidium* and *Giardia lamblia* among children and is available in a liquid formulation (**BI** for uninfected children and **CIII** HIV-infected children). An Egyptian clinical trial among 100 HIV-uninfected patients, half of them children, randomized patients to a 3-day course of nitazoxanide or placebo. Nitazoxanide therapy reduced the duration of both diarrhea and oocyst shedding; among children, clinical response was 88% with nitazoxanide and 38% with placebo. No substantial adverse events were reported, and adverse events that were reported were similar in the treatment and placebo groups in this study. A study in Zambia among 100 children aged 12-35 months, half HIV-infected, reported a clinical response of 56% with treatment compared with 23% with placebo among HIV-uninfected children, but among HIV-infected children, the drug was no more effective than placebo. However, in a study among HIV-infected adults in Mexico, 14 days of nitazoxanide resulted in 67% response using 1,000 mg twice daily and 63% using 500 mg twice daily, compared with 25% with placebo. One study among HIV-infected adults demonstrated clinical response in patients with CD4 cell count >50/microliter but not those with CD4 cell count <50/microliter. The recommended dose for children is 100 mg orally twice daily for children aged 1-3 years and 200 mg twice daily for children aged 4-11 years. A tablet preparation is not yet approved.

Certain specialists recommend paromomycin (25-35 mg/kg body weight/day orally in 2-4 divided doses; maximum dose: 500 mg four times daily) for the treatment of cryptosporidiosis in HIV-infected children (**CIII**). However, in a placebo-controlled trial in HIV-infected adults, paromomycin was no more effective than placebo for the treatment of symptomatic cryptosporidiosis.

Azithromycin has demonstrated some activity against *C. parvum* infection in a limited number of HIV-infected children (**CIII**). An azithromycin regimen of 10 mg/kg per day on day 1 and 5 mg/kg per day on days 2-10 was successful in rapidly resolving enteric symptoms in three of four HIV-infected children with cryptosporidiosis. Oral hyperimmune bovine colostrum and oral immune globulin

have variable benefits among immunocompromised patients with cryptosporidiosis (**CIII**).

For treatment of microsporidia infection, albendazole (dosage for person weighing <60 kg is 7.5 mg/kg orally twice daily; maximum dose: 400 mg orally twice daily) decreases diarrhea, sometimes with eradication of the organism (**AII**). Albendazole appears to be more effective for cases caused by *Encephalitozoon intestinalis* and other microsporidia species but is not active against *Enterocytozoon bieneusi*. Nitazoxanide has been used for treatment of *Enterocytozoon bieneusi* infection among HIV-infected adults.

Fumagillin® (Sanofi-Synthelabo Laboratories, Gentilly, France) is an antibiotic derived from the fungus *Aspergillus fumigatus*, which has been used to treat microsporidiosis in animals and humans. In a placebo-controlled study of immunocompromised adults (including HIV-infected adults) with *Enterocytozoon bieneusi* microsporidiosis, fumagillin (20 mg/dose orally three times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidial spores, which was not observed in placebo patients. Dose-related bone marrow toxicity was the principal adverse effect of fumagillin, with reversible thrombocytopenia and neutropenia being the most frequent adverse events. No data are available on use of fumagillin among HIV-infected children (**CIII**), and the drug is not available in the United States. Ocular infections caused by microsporidia among HIV-infected adults have been treated topically with fumagillin eye drops prepared from Fumidil-B, a commercial product (Mid-Continent Agrimarketing, Inc., Olathe, KS) used to control a microsporidial disease of honeybees.

***Mycobacterium tuberculosis* (TB)**

Principles for treatment of TB in the HIV-infected child are the same as for the HIV-uninfected child. However, optimal therapy has not been defined, and modified treatment durations, schedules, and medications are recommended for specific instances. Because of overlapping drug toxicities, children being treated for both HIV and TB should be managed by a specialist with expertise in treating both these conditions (**AIII**).

Because of the high risk for dissemination among children aged <4 years, TB treatment should be initiated as soon as the diagnosis of TB is suspected (**AIII**). Although the optimal timing of initiation of antiretroviral therapy during TB treatment is unknown, in the setting of antiretroviral naive HIV-infected children, treatment of TB should be initiated 4-8 weeks before initiating antiretroviral medications to improve adherence and better differentiate potential side effects (**BIII**). For children already receiving antiretroviral therapy who have had TB diagnosed, the child's antiretroviral regimen should be reviewed and altered, if needed, to ensure optimal treatment for both TB and HIV and to minimize potential toxicities and drug-drug interactions (**BIII**).

The major problem limiting successful treatment is inadequate adherence to prescribed treatment regimens. Use of directly observed therapy (DOT) decreases the rates of relapse, treatment failures, and drug resistance. Therefore, DOT is recommended for treatment of children and adolescents with TB in the United States (**AII**). For the first 2 months of treatment, DOT should be administered

daily (induction phase). After this, DOT is usually given two to three times weekly (continuation phase). For patients on rifampin- or rifabutin-based regimens and who have severe immunosuppression, three-times weekly regimens are preferred because of concerns about development of rifamycin resistance by *M. tuberculosis* (**BII**). However, data on the efficacy of three-times weekly regimens among children are limited.

Initial empiric treatment of active disease (induction phase) should generally consist of a 4-drug regimen (isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin) to allow for the possibility of a drug-resistant organism (**AI**). Ethionamide can be used as an alternative to ethambutol in cases of TB meningitis because ethionamide has better CNS penetration than ethambutol (**AIII**).

Subsequent modifications of therapy should be based on susceptibility testing if possible. The drug susceptibility pattern from the isolate of the adult source case might help guide treatment in cases where an isolate is not available from the child. If the organism is susceptible to isoniazid, rifampin, and pyrazinamide during the 2-month period of induction therapy, ethambutol can be discontinued and induction therapy completed using 3 drugs (**AI**).

Following the 2-month induction phase, for treatment of *M. tuberculosis* known to be sensitive to isoniazid and rifampin, therapy is continued with isoniazid and rifampin to complete therapy (**AI**); daily or intermittent (2-3 times weekly) therapy is acceptable. However, children with severe immunosuppression should receive either daily or thrice weekly treatment during the continuation phase, because TB treatment regimens with once- or twice-weekly dosing have been associated with an increased rate of acquisition of rifamycin resistance among HIV-infected adults with low CD4 cell counts (<100 cells/microliter) (**AII**).

Many clinicians report high rates of treatment failure and relapse when only 6 months of treatment is administered (the recommended duration of therapy for children without HIV infection). For HIV-infected children with active pulmonary disease, the minimum recommended duration of anti-tuberculous drug treatment is 9 months; for children with extrapulmonary disease involving the bones or joints, CNS, or miliary disease, the minimum recommended duration of treatment is 12 months (**AIII**). These recommendations assume that the organism is susceptible to the medications, that compliance with the medications has been assured, and that the child has had a clinical and microbiologic response to therapy.

For treatment of drug-resistant TB, a minimum of three drugs should be administered, including at least 2 bactericidal drugs to which the isolate is susceptible (**AII**). Regimens can include three to six drugs with varying levels of activity. Children infected with multidrug-resistant TB (e.g., resistance to at least isoniazid and rifampin) should be managed in consultation with an expert in this condition (**AIII**). If the strain is resistant only to isoniazid, isoniazid should be discontinued and the patient treated with 9-12 months of a rifampin- or rifabutin-containing regimen (e.g., rifampin, pyrazinamide and ethambutol (**BII**); ethionamide or streptomycin can be substituted for ethambutol if the *M. tuberculosis* isolate is sensitive to these agents). If the strain is resistant only to rifampin, risk for relapse and treatment failure is increased. Rifampin should be

discontinued and a 2-month induction phase of isoniazid, pyrazinamide, ethambutol and streptomycin administered, followed by an additional continuation phase of isoniazid, pyrazinamide, and ethambutol to complete a minimum of a 12-month course of therapy, with the exact length of therapy based on clinical and radiologic improvement (**BIII**). Among older adolescents with rifampin monoresistant strains, isoniazid, ethambutol, and a fluoroquinolone can be administered, with pyrazinamide added for the first 2 months (**BIII**); an injectable agent (e.g., aminoglycoside such as streptomycin or amikacin) also can be included in the first 2-3 months for patients with severe disease (**BIII**). When the strain is resistant to isoniazid and rifampin (multidrug-resistant TB), therapeutic regimens must be individualized based on the resistance pattern, relative activities of the drugs, extent of disease, and any comorbid conditions. Therapy frequently requires 12-24 months.

Isoniazid (10-15 mg/kg body administered orally once daily [maximum dose: 300 mg/day]) is available as syrup, but certain specialists advise against using it because the syrup is unstable and frequently causes diarrhea. When isoniazid is administered in a dosage exceeding 10 mg/kg in combination with rifampin, the incidence of hepatic toxicity might be increased. Pills can be pulverized at the time of administration and mixed with a small amount of appealing food immediately before giving it to the child. Dose for two-times weekly administration is 20-30 mg/kg/dose (maximum dose: 900 mg).

Gastric upset during the initial weeks of isoniazid treatment occurs frequently. Hepatotoxicity is the most common adverse effect and includes subclinical hepatic enzyme elevation and clinical hepatitis that can be reversible when drug is discontinued or rarely progresses to hepatic failure. Hepatotoxicity is less frequent in children than in adults. Transient asymptomatic serum transaminase elevations have been noted in 3%-10% and clinical hepatitis in <1% of children receiving isoniazid, although <1% of children required treatment discontinuation. However, the rate of hepatotoxicity might be higher in children on multiple hepatotoxic medications. Other toxicities reported with isoniazid include peripheral neuritis, mild CNS effects, and rare hypersensitivity reactions. Pyridoxine is recommended for children and adolescents on meat- and milk-deficient diets and children with nutritional deficiencies, including all symptomatic HIV-infected children (**AII**).

Rifampin (10-20 mg/kg administered orally once daily [maximum dose: 600 mg/day]) is available only as a capsule. It can be administered by opening the capsule and sprinkling the contents on food. Alternatively, a suspension can be formulated by the pharmacy, although the stability of the *ad hoc* suspension is unknown. Dose for twice weekly administration is 10-20 mg/kg per dose (maximum dose: 600 mg).

Rifampin is excreted in urine, tears, sweat, and other body fluids and colors them orange; contact lenses may be stained. The most common adverse reaction to rifampin therapy is gastrointestinal upset. Other reactions include skin rash, hepatitis, thrombocytopenia, and cholestatic jaundice. An influenza-like syndrome, hemolytic anemia, and acute renal failure have been reported among adults receiving high doses of rifampin.

Rifampin induces hepatic cytochrome P450 enzymes and can accelerate clearance of drugs metabolized by the liver (e.g., protease inhibitors and non-nucleoside

reverse transcriptase inhibitors), resulting in subtherapeutic levels of the drug. As a result, concurrent administration of rifampin and single protease inhibitors, with the exception of ritonavir, is not recommended (**EII**). Coadministration of ritonavir-boosted saquinavir, with 400 mg ritonavir boosting, with rifampin is possible, but low-dose ritonavir-boosted dual protease inhibitor regimens should not be used. Concurrent administration of rifampin with the non-nucleoside reverse transcriptase inhibitor delavirdine also is contraindicated because of similar drug interactions (**EII**). However, concomitant administration of rifampin with efavirenz (and perhaps nevirapine) is possible. Rifampin- and nevirapine-containing regimens should be used only when no other options are available and close clinical and virologic monitoring can be performed because of the decrease in nevirapine levels that can occur with concomitant administration.

Rifabutin (10-20 mg/kg administered orally once daily) is a suitable alternative to rifampin in children on HAART that proscribes the use of rifampin; however, experience in children is limited (**BIII**). Major toxicities of rifabutin include leukopenia, gastrointestinal upset, polyarthralgias, rash, elevated transaminases, and skin and secretion discoloration (pseudojaundice). Anterior uveitis has been reported among adults and children receiving rifabutin as prophylaxis or a part of a combination regimen for treatment usually when administered at higher doses.

Rifabutin also increases hepatic metabolism of many drugs but is a less potent inducer of cytochrome P450 enzymes than rifampin and has fewer problematic drug interactions than rifampin. However, adjustments in doses of rifabutin and the coadministered antiretroviral drugs might be necessary for certain combinations. Coadministration of rifabutin with certain protease inhibitors can result in increased rifabutin concentration and thus potential toxicity; therefore, a decrease in rifabutin dose by 50% is required when coadministered with ritonavir, indinavir, nelfinavir, amprenavir, or ritonavir-boosted saquinavir. An increased dose (by 50%-100%) of rifabutin is needed when coadministered with efavirenz because of decreased rifabutin levels with coadministration. Rifabutin should not be coadministered with delavirdine or hard gel capsule saquinavir without ritonavir boosting because of substantial decreases in the concomitant protease inhibitor drug levels (**EII**). Other drugs that inhibit hepatic metabolism (e.g., fluconazole) also can increase concentrations of rifabutin and consequent toxicity and might require dose adjustment or discontinuation of rifabutin.

Pyrazinamide (20-40 mg/kg/day is administered orally once daily [maximum dose: 2 g/day]) is available only as a scored tablet. It is generally administered during the first 2 months of TB therapy. If pyrazinamide is to be continued on a two- to three-times-weekly schedule, it should be administered at a dose of 50-70 mg/kg/dose (maximum dose: 2 g). Adverse effects include hepatotoxicity and hyperuricemia, arthralgias, skin rash, and gastrointestinal intolerance.

Ethambutol (15-25 mg/kg administered orally in single oral dose [maximum dose: 1.0 g]) is available only as a scored tablet. Although not approved for use among children because of concern for optic nerve toxicity that might not be easily recognizable with pediatric use, it has been used in children without toxicity (**BIII**). Dose for twice weekly administration is 50 mg/kg per dose (maximum dose: 1.0 g). The major toxicity is optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, which is usually reversible and rare at doses of 15 mg/kg among children with normal renal function. Children

receiving ethambutol should have monthly monitoring of visual acuity and color discrimination if possible (**AIII**). Other toxicities include headache, nausea, peripheral neuropathy, rash, and hyperuricemia.

Secondary drugs used in treatment of resistant TB have not been well studied in children. These medications should be used in consultation with a TB specialist. Ethionamide (15-20 mg/kg administered orally divided into 2-3 doses per day [maximum dose: 1.0 g/day]) is available only in tablet formulation. Data are unavailable to support intermittent (e.g. twice or three times weekly) dosing of this drug. Ethionamide might be useful for children with drug-resistant TB or TB meningitis because the drug achieves increased concentration in CSF. Nausea, vomiting, loss of appetite, and abdominal pain are the most common adverse effects. Other adverse effects include hepatitis, arthralgias, gynecomastia, photosensitive dermatitis, and a metallic taste in the mouth. Hypothyroidism has been reported with ethionamide use, and periodic (e.g., monthly) monitoring of thyroid hormone serum concentrations is recommended (**AIII**).

Streptomycin (20-40 mg/kg/day administered intramuscularly once daily [maximum dose: 1 g/day]) is an alternative drug that can be substituted for ethambutol (**BIII**). It also is used in combination quadruple therapy with rifampin, isoniazid, and pyrazinamide for CNS TB (meningitis and tuberculoma). Dosage for twice weekly administration is 20 mg/kg per dose intramuscularly (maximum dose: 1 g). If streptomycin is not available, kanamycin (15-30 mg/kg administered intramuscularly once daily [maximum dose: 1 g/day]) or amikacin (15-30 mg/kg administered intravenously or intramuscularly once daily [maximum dose: 1 g/day]) are active against most strains of streptomycin-resistant *M. tuberculosis*. Amikacin has the advantage of a lower rate of ototoxicity and has largely replaced kanamycin in the treatment of adults. Major adverse effects of aminoglycoside drugs are oto- and nephrotoxicity. Periodic audiometry, monitoring of vestibular function (if possible), and blood urea nitrogen and creatinine are recommended.

Capreomycin (15-30 mg/kg administered intravenously or intramuscularly once daily [maximum dose: 1 g/day]) is a secondary drug used for drug-resistant TB. The major adverse effect is toxicity to the eighth cranial nerve. Renal toxicity also might be seen, with electrolyte disturbances secondary to tubular damage and elevated serum creatinine. Monitoring of hearing with audiograms monthly, periodic examinations of vestibular function, and regular monitoring of blood urea nitrogen and creatinine are recommended (**AIII**).

Quinolones such as ciprofloxacin (10-15 mg/kg administered orally twice daily [maximum dose: 1.5 g/day]), ofloxacin (400-800 mg total given orally once daily in adults [maximum dose: 800 mg/day]) levofloxacin (500-1,000 mg administered orally once daily in adults) and moxifloxacin (400 mg administered orally once daily in adults) can be used. Adverse effects of quinolones include gastrointestinal upset, diarrhea, rash, and headache. Cartilage damage has been observed with use of the fluoroquinolone drugs in animals and, theoretically, these drugs could have an effect on growing cartilage in children; they are not approved for persons aged <18 years and use in younger persons requires an assessment of potential risks and benefits (**CIII**). Ciprofloxacin has had the greatest use among children and appears to be well tolerated and not associated with arthropathy.

Cycloserine (10-20 mg/kg administered orally once daily [maximum dose: 1 g]) is another second-line antimycobacterial that might be needed for treatment of drug-resistant infections. The major adverse reactions are emotional and behavioral disturbances, and periodic assessment of mental status is recommended. Convulsions and peripheral neuropathy can occur, especially if administered with isoniazid, and coadministration of pyridoxine (150 mg/day) is recommended (**AII**).

Para-amino salicylic acid (200-300 mg/kg administered orally divided into 3 or 4 daily doses [maximum dose: 10 g/day]) also can be used for treatment of drug-resistant TB. The adverse effects of the drug are predominantly gastrointestinal (nausea, vomiting, and diarrhea). Hypersensitivity reactions occur in 5%-10% of persons, and hepatitis can occur. Hepatic enzyme monitoring is recommended (**AIII**). Thiacetazone can cause severe and often fatal reactions among HIV-infected children, including severe rash and aplastic anemia, and should not be used (**EIII**).

Unlike the majority of children without HIV infection, HIV-infected children on anti-TB medications should have liver enzymes obtained at baseline and monthly for the first few months of therapy (**AIII**). If symptoms of drug toxicity develop, a physical examination and repeat liver enzyme measurement should be performed (**AIII**). Mild elevations in serum transaminases (e.g., 2-3 times upper limit of normal) do not require discontinuation of drugs if other findings are normal (**AII**).

Adjunctive treatment with corticosteroids is indicated for children with tuberculous meningitis; dexamethasone lowers mortality and long-term neurologic impairment (**AII**). These drugs might be considered for children with pleural or pericardial effusions, severe miliary disease, and substantial endobronchial disease (**BIII**). Appropriate antituberculous therapy must be administered concomitantly. Most experts use 1 to 2 mg/kg/day of prednisone or its equivalent for 6-8 weeks.

Monthly monitoring of clinical and bacteriologic response to therapy is important (**AII**). For children with pulmonary TB, chest radiographs should be obtained after 2-3 months of therapy to evaluate response (**AIII**). Hilar adenopathy might persist for as long as 2-3 years despite successful antituberculous therapy, and a normal radiograph is not a criterion to discontinue therapy. Follow-up radiographs after completion of therapy are not necessary unless clinical symptoms recur.

An immune reconstitution syndrome in patients receiving anti-TB therapy in the setting of HAART has been reported in HIV-infected adults. New onset of systemic symptoms, especially high fever, expanding CNS lesions, and worsening adenopathy, pulmonary infiltrates, or pleural effusions have been reported in the setting of HAART up to several months after starting TB therapy. Persons with mild-to-moderate symptoms of immune reconstitution syndrome have been treated symptomatically with nonsteroidal anti-inflammatory drugs while continuing anti-TB and HIV therapies. In certain cases, use of systemic corticosteroids steroids for 1-2 weeks results in improvement while continuing to receive TB/HIV therapies (**CIII**).

***Mycobacterium avium* Complex (MAC) Disease**

Treatment of disseminated MAC infection should be done in consultation with a pediatric infectious disease specialist with expertise in pediatric HIV infection (**AIII**). Combination therapy with a minimum of 2 drugs is recommended (**AI**). Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.

The most effective way to prevent disseminated MAC among HIV-infected children is to preserve immune function through use of effective antiretroviral therapy. In addition, improved immunologic status is important for control of MAC disease among children with disseminated disease; potent antiretroviral therapy should be initiated among children with MAC disease who are antiretroviral-naive. However, the optimal time to start HAART in this situation is unknown; certain clinicians treat MAC 1-2 weeks before starting HAART to try to minimize the occurrence of immune reconstitution syndrome, although whether this makes a difference is unknown (**CIII**). HAART should be continued and optimized for those already being treated. Prolonged survival among HIV-infected adults with MAC has been associated with receiving therapy that included clarithromycin and receiving combination antiretroviral therapy that included a protease inhibitor.

Initial empiric therapy should include at least two drugs: clarithromycin or azithromycin plus ethambutol (**AI**). Certain specialists use clarithromycin as the preferred first agent, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern (**AII**).

Rifabutin can be added as a third drug to the clarithromycin/ethambutol regimen, particularly in patients with more severe symptoms or disseminated disease (**AI**). A study in adult patients demonstrated a survival benefit with the addition of rifabutin to clarithromycin plus ethambutol. Drugs that can increase cytochrome P3A activity (e.g., rifabutin) can lead to increased clearance of other drugs (e.g., protease inhibitors and non-nucleoside reverse transcriptase inhibitors), and increased toxicity might be observed with concomitant administration of drugs competing for the same metabolic pathways. Therefore, drug interactions should be checked carefully, and more intensive toxicity monitoring might be warranted if such drugs are given concomitantly (**AIII**). A decrease in rifabutin dosage by 50% is required when coadministered with ritonavir, indinavir, nelfinavir, amprenavir, or ritonavir-boosted saquinavir; an increased dose (by 50%-100%) of rifabutin is needed when coadministered with efavirenz. Rifabutin should not be coadministered with delvaridine or hard gel capsule saquinavir without ritonavir boosting because of substantial decreases in the concomitant protease inhibitor drug levels (**EII**).

Additional drugs can be considered depending on severity of illness. In a patient with severe illness, if rifabutin cannot be administered, ciprofloxacin, levofloxacin and amikacin or streptomycin have been used (**CIII**). In one study in HIV-infected adults, amikacin did not provide additional clinical or microbiologic benefit in a clinical trial of disseminated MAC therapy. In other studies, clofazamine was not associated with clinical or microbiologic benefit and was associated with increased mortality and is therefore not recommended (**EII**).

Clarithromycin is administered at a dose of 7.5-15.0 mg/kg body weight orally twice daily (maximum dose: 500 mg twice daily) (**AI**). Major toxicities include

nausea, diarrhea, and abdominal pain. Uncommon toxicities include headache, leukopenia, altered taste, and elevated transaminases. Clarithromycin can inhibit hepatic metabolism of other drugs cleared by the liver, thus potential drug interactions with concomitantly administered drugs need to be considered.

Azithromycin is administered at a dose of 10-12 mg/kg orally once daily (maximum dose: 500 mg daily) and can be given as an alternative to clarithromycin (**AII**). Major toxicities include nausea, diarrhea, abdominal pain, and possible ototoxicity; uncommon adverse effects include headache, leukopenia, and elevated transaminases. Azithromycin has a minor effect on hepatic metabolism of other drugs and has less drug interactions than clarithromycin.

Ethambutol is administered at a dose of 15-25 mg/kg and is administered in single oral dose (maximum dose: 1.0 g) (**AI**). It is available only as a scored tablet. Although not approved for use among children because of concern for optic nerve toxicity that might not be easily recognizable with pediatric use, it has been used among children without a high incidence of toxicity. The major toxicity is optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, which is usually reversible and is rare at doses of 15 mg/kg. Children receiving ethambutol should have monthly monitoring of visual acuity and color discrimination if possible (**AII**). Other toxicities include headache, nausea, peripheral neuropathy, rash, and hyperuricemia.

Rifabutin is administered at a dose of 10-20 mg/kg orally once daily (maximum dose: 300 mg/day) (**AI**). The drug is not available in a liquid formulation, but a suspension (10 mg/mL in a cherry or simple syrup) can be formulated from the contents of capsules. Major toxicities of rifabutin include leukopenia, gastrointestinal upset, polyarthralgias, rash, elevated transaminases, and skin and secretion discoloration (pseudojaundice). Anterior uveitis has been reported in adults and children receiving rifabutin as prophylaxis or a part of a combination regimen for treatment, usually when administered at higher doses.

Ciprofloxacin is administered at a dose of 20-30 mg/kg intravenously or orally once daily (maximum dose: 1.5 grams). Adverse effects of quinolones include gastrointestinal upset, diarrhea, rash, and headache. Cartilage damage has been observed with use of the fluoroquinolone drugs in animals, and theoretically, these drugs can have an effect on growing cartilage in children. They are not approved for persons aged <18 years and use in younger persons requires an assessment of potential risks and benefits (**CIII**). Of the quinolone drugs, ciprofloxacin has had the greatest use among children and appears to be well-tolerated and not associated with arthropathy.

Amikacin can be administered at a total daily dose of 15-30 mg/kg/day divided every 12-24 hours (maximum dose: 1.5 grams) (**CIII**). Amikacin is available only for intravenous administration and might be useful as a second-line agent. Ototoxicity and renal toxicity are adverse effects.

Most patients demonstrate substantial clinical improvement during the first 4-6 weeks of therapy. Microbiologic response can be monitored by blood cultures every 4 weeks during initial therapy (**BIII**). However, elimination of the organism from the blood might require up to 12 weeks of effective therapy. An immune

reconstitution syndrome in patients receiving MAC therapy in the setting of HAART has been reported among HIV-infected adults. New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal lymphadenitis (cervical, thoracic, or abdominal) associated with preexisting but relatively asymptomatic MAC infection, has been seen after starting HAART. Before initiation of HAART among HIV-infected children with low CD4+ cell counts, consideration should be given for an assessment for MAC and treatment if MAC is identified. However, recent data indicate that MAC prophylaxis with azithromycin did not prevent the development of immune reconstitution disease. Children with moderate symptoms of immune reconstitution syndrome can be treated symptomatically with nonsteroidal anti-inflammatory drugs or, if unresponsive to nonsteroidals, a short course (e.g., 4 weeks) of systemic corticosteroid therapy while continuing to receive HAART (**CIII**).

Among HIV-infected children with MAC disease, after initial therapy, lifetime chronic suppressive maintenance therapy for MAC (secondary prophylaxis) is required. Although discontinuation of secondary prophylaxis in adults receiving HAART has been evaluated, the safety of discontinuation of secondary prophylaxis after immunologic recovery with HAART among children has not been studied extensively.

Serious and Recurrent Bacterial Infections

The local prevalence of resistance to common infectious agents (i.e., penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*) and the recent use of prophylactic or therapeutic antibiotics should be considered when initiating empiric therapy. When the organism is identified, antibiotic susceptibility testing should be performed and therapy based on the results of susceptibility testing (**AII**).

HIV-infected children whose immune systems are not seriously compromised (Center for Disease Control [CDC] Immune Class I) and who are not neutropenic can be expected to respond similarly to HIV-uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms (**AIII**). For example, for HIV-infected children outside of the neonatal period with suspected community-acquired bacteremia, bacterial pneumonia, or meningitis, empiric therapy with an extended-spectrum cephalosporin such as ceftriaxone (80-100 mg/kg body weight in 1 or 2 divided doses [maximum daily adult dose: 4 g]), cefotaxime (150-200 mg/kg divided into 3 or 4 doses [maximum daily adult dose: 8-10 g]), or cefuroxime (100-150 mg/kg divided into 3 doses [maximum daily adult dose: 4-6 g]) is reasonable until culture results are available (**AIII**).

Initial empiric therapy of HIV-infected children with suspected catheter sepsis should include coverage for both gram-positive and enteric gram-negative organisms, such as ceftazidime (125-150 mg/kg divided into 3 doses [maximum daily adult dose: 6 g]), which has anti-*Pseudomonas* activity, and vancomycin (40-60 mg/kg divided into 4 doses [maximum daily adult dose: 2-4 g]) to cover methicillin-resistant *S. aureus* (**AIII**). Severely immunocompromised HIV-infected children with invasive or recurrent bacterial infections might require expanded empiric antimicrobial treatment covering a broad range of resistant organisms

similar to that chosen for suspected catheter sepsis pending results of diagnostic evaluations and cultures (**AIII**).

HIV-infected children aged <5 years should receive Haemophillus influenzae type B (Hib) and heptavalent pneumococcal conjugate vaccines (**AII**). In a placebo-controlled trial of a 9-valent pneumococcal conjugate vaccine among South African children, although vaccine efficacy was somewhat lower among children with HIV infection than those without (65% versus 85%, respectively), the incidence of invasive pneumococcal disease was substantially decreased among HIV-infected vaccine recipients. HIV-infected children aged >2 years also should receive the 23-valent pneumococcal polysaccharide vaccine ($\geq$2 months after their last conjugate vaccine dose), with a single revaccination with the pneumococcal polysaccharide vaccine 3-5 years later if the child is aged $\leq$10 years or after 5 years if the child is aged >10 years (**AIII**).

Syphilis

Data are insufficient about whether infants who have congenital syphilis and whose mothers are coinfected with HIV require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants. Some studies in adults have shown a lag in serological improvement in appropriately treated patients with HIV infection.

Infants should be treated if mothers have untreated or inadequately treated syphilis (including treatment with erythromycin or any other nonpenicillin regimen) or no documentation of having received treatment; received treatment $\leq$4 weeks before delivery; been treated with penicillin but titers did not decrease by four-fold; or have four-fold or greater increase in nontreponemal antibody titer suggesting relapse or reinfection (**AII**). Infants should be treated regardless of maternal history if an abnormal examination consistent with congenital syphilis, positive darkfield or fluorescent antibody test of body fluid(s), or serum quantitative nontreponemal serologic titer that is the same or four-fold greater than maternal titer are observed (**AII**).

Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G at a dose of 100,000-150,000 units/kg/day, administered as 50,000 units/kg body weight/dose intravenously every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days (**AII**). If congenital syphilis is diagnosed after 1 month of life, the dose of aqueous penicillin G should be increased to 200,000-300,000 units/kg intravenously every 6 hours for 10 days (**AII**). An alternative to aqueous penicillin G is procaine penicillin G at a dose of 50,000 units/kg/dose intramuscularly/day in a single dose for 10 days (**BII**). However, aqueous penicillin G is preferred because of its higher penetration into the CSF.

Asymptomatic infants born to mothers who have had adequate treatment and response to therapy and normal physical examination and CSF findings but who have a serum quantitative nontreponemal serologic titer that is the same or four-fold higher than maternal titer might be treated with a single dose of benzathine penicillin G 50,000 units/kg/dose intramuscularly with careful clinical and serologic follow-up (**BII**). However, certain health-care providers would treat such infants with the standard 10 days of aqueous penicillin because physical

examination and laboratory test results cannot definitively exclude congenital syphilis in all cases (**BII**).

Infants with treated congenital syphilis should be examined at age 1, 2, 3, 6, and 12 months, with serologic nontreponemal tests performed at age 3, 6 and 12 months after conclusion of treatment or until results become nonreactive (**AIII**). If initial CSF examination was abnormal, repeat lumbar puncture should be conducted every 6 months until results are normal. Nontreponemal antibody titers should decline by age 3 months and be nonreactive by age 6 months if the infant was adequately treated or not infected (e.g., passive antibody transfer from mother). Children with increasing titers or persistently positive titers (even if low levels) at age 6-12 months should be evaluated and considered for treatment (**AIII**). Children with congenital syphilis who are also HIV-infected might take longer to become nonreactive and might require retreatment.

Acquired syphilis is treated with a single dose of benzathine penicillin G 50,000 units/kg intramuscularly for early stage disease (e.g., primary, secondary, and early latent disease) (**AII**). For late latent disease, 3 doses of benzathine penicillin G 50,000 units/kg should be administered intramuscularly once weekly for 3 doses (**AIII**). Alternative therapies (e.g., doxycycline, ceftriaxone, or azithromycin) have not been evaluated among HIV-infected patients and should not be used as first-line therapy (**EIII**). Neurosyphilis should be treated with aqueous penicillin G 200,000-300,000 units/kg intravenously every 6 hours (maximum dose: 18-24 million units/day) for 10-14 days (**AII**).

Children and adolescents with acquired syphilis should have clinical and serologic response monitored at age 3, 6, 9, 12, and 24 months after therapy (**BIII**). Nontreponemal test titers should decline by at least four-fold by 6-12 months after successful therapy. If initial CSF examination was abnormal, repeat lumbar puncture should be conducted at 3 and 6 months after therapy and then every 6 months until results are normal and Venereal Disease Research Laboratory (VDRL) is negative.

***Candida* Infections**

Oropharyngeal Candidiasis (OPC)

1. Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral polyenes (such as nystatin or amphotericin B suspension). Clotrimazole is administered as 10 mg troches used orally 4-5 times daily for 14 days (**BII**). Resistance to clotrimazole can develop as a consequence of previous exposure to clotrimazole itself or to other azole drugs; resistance correlates with refractory mucosal candidiasis. Nystatin suspension is administered as 400,000-600,000 U/mL (4-6 mL four times daily) or 1-2 flavored 200,000 U pastilles 4-5 times daily for 7-14 days (**BII**). No adverse effects have been reported, but bitter taste might contribute to poor adherence.
2. Systemic therapy with one of the oral azoles (fluconazole, ketoconazole or itraconazole) also is effective for initial treatment of OPC. Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC among infants and is easier to administer to children than the topical therapies (**AI**).

Itraconazole solution is comparable in efficacy to fluconazole, although it might be less well tolerated (**AI**).

3. If initial therapy is with topical therapy, failure or relapse should be treated with oral fluconazole (3-6 mg/kg administered once a day for 7-14 days orally) or itraconazole cyclodextrin oral solution (2.5 mg/kg body weight/dose administered twice daily for 7-14 days [maximum dose: 200-400 mg/day]) (**AI**).
4. Itraconazole capsules and oral solution should not be used interchangeably because drug exposure is greater with the oral solution when the same dose of drug is administered and absorption of the capsule formulation is variable. Therefore, itraconazole capsules should be considered second-line therapy (**DII**). Because absorption of itraconazole solution is enhanced by presence of gastric acid, it should be taken without food when possible; in contrast, itraconazole capsules should be administered with food.
5. Ketoconazole tablets also can be used to treat OPC as a dose of 5-10 mg/kg/day in 1-2 divided doses for 14 days, but it might be less effective than fluconazole or itraconazole solution because of more variable absorption. As a result, it is second-line therapy for OPC (**DII**).
6. The azole drugs have relatively low rates of toxicity but have substantial drug interactions that can limit their use. Because of their ability to inhibit the cytochrome P-450-dependent hepatic enzymes (ketoconazole having the strongest inhibitory effect), the azole drugs can have substantial interactions with other drugs undergoing hepatic metabolism. This can result in decreased plasma concentration of the azole because of increased metabolism induced by the coadministered drug, or development of unexpected toxicity from the coadministered drug because of increased plasma concentrations secondary to azole-induced alterations in hepatic metabolism. The potential for drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy (**AIII**).
7. The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting, and are most often reported with ketoconazole (10%-40% of patients). Skin rash and pruritus might be observed with all drugs; rare cases of Stevens-Johnson syndrome have been reported with fluconazole therapy. All drugs are associated with asymptomatic increases in transaminases (1%-13% of patients) and, less frequently, hepatitis. Hematologic abnormalities have been reported, including hemolytic anemia with ketoconazole and thrombocytopenia and leucopenia with itraconazole. Ketoconazole has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia. Fluconazole has been associated with alopecia in the scalp and pubic area.
8. Fluconazole-refractory OPC will respond to itraconazole solution in approximately 50%-60% of patients (**BII**). Amphotericin B oral suspension at a dose of 1 mL four times a day of 100 mg/mL suspension also has been used for fluconazole-refractory OPC, although the response rate is less than observed with itraconazole solution (**BII**). Intravenous amphotericin B (0.3-0.5 mg/kg/day) has been used as a last resort among patients with severe, refractory OPC (**BII**).

Esophageal Diseases

1. Systemic therapy, generally with fluconazole or itraconazole, is essential for esophageal disease and should be initiated empirically among HIV-infected children with OPC and esophageal symptoms (**AII**). In the majority of patients, symptoms should resolve within days of the start of effective therapy. Fluconazole (6 mg/kg/day administered once on day 1, then 3-6 mg/kg administered once a day for a minimum of 14-21 days) is superior to ketoconazole for treatment of candidal esophagitis (**AI**).
2. Itraconazole cyclodextrin oral solution (pediatric dosage: 2.5 mg/kg/dose administered twice a day or 5.0 mg/kg/dose administered once daily for a minimum of 14-21 days) is as efficacious as fluconazole for esophageal disease (**AI**). Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution. Itraconazole capsules are generally ineffective for treatment of esophageal disease (**DII**).
3. Low-dose intravenous amphotericin B (0.3 mg/kg/day for a minimum of 7 days) also is effective and can be used in patients with otherwise refractory disease (**BII**).
4. Voriconazole has been used in a limited number of children without HIV infection to treat invasive fungal infections, including some with esophageal candidiasis or fungemia. Voriconazole was generally administered as a loading dose of 6 mg/kg intravenously every 12 hours on day 1, followed by 4 mg/kg intravenously every 12 hours thereafter. After the child stabilized, administration was changed to oral (100 mg twice a day for children weighing <40 kg, and 200 mg twice a day for children $\geq$40 kg) to complete therapy (median duration of therapy: 93 days). Because of limited experience among children, data are insufficient to recommend use of this drug for esophageal or disseminated candidiasis (**CIII**).
5. Side effects of voriconazole are similar to the other azole drugs. In addition, dose-related, reversible visual changes (e.g., photophobia and blurry vision) have been reported in approximately 30% of patients receiving voriconazole. Cardiac arrhythmias and renal abnormalities including nephritis and acute tubular necrosis also have been reported with voriconazole use.
6. Caspofungin, an echinocandin inhibitor of fungal (1,3)-beta-D-glucan synthetase inhibitor, is effective and comparable to amphotericin B and fluconazole for treatment of esophageal *Candida* infections and comparable to amphotericin B for treatment of candidemia in adults. It is only available for intravenous administration because it has very limited bioavailability. Experience is limited with caspofungin in children, and a definitive pediatric dose has not been defined. Therefore, data are insufficient to recommend use of this drug for esophageal or invasive candidiasis in children (**CIII**).
7. In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated, and only three patients had adverse events that might have been related to the drug (hypokalemia in all three children, elevated bilirubin in two, and decreased hemoglobin and elevated alanine aminotransferase in one). In this study, children weighing <50 kg received doses ranging from 0.8-1.6 mg/kg daily, and those weighing >50 kg received adult dosing. Preliminary pharmacokinetic data on caspofungin among children indicate that a daily intravenous dose of 1.5 mg/kg or 50 mg/m^2/day is required to provide exposure similar to that seen in adults receiving 50 mg/day.

Invasive Disease

1. Central venous catheters should be removed when feasible among HIV-infected children with fungemia (**AII**).
2. Conventional amphotericin B (sodium deoxycholate complex) is the drug of choice for most invasive candidal infections in children (**AI**). The recommended amphotericin B regimen is 0.5-1.5 mg/kg administered once daily intravenously. Amphotericin B is administered in 5% dextrose in water to give a final concentration of 0.1 mg/mL and is administered once daily intravenously over 1-2 hours. Among patients with azotemia, hyperkalemia, or who are receiving high dose (>1 mg/kg), a longer infusion time of 3-6 hours is recommended (**BIII**).
3. Among patients with mild-to-moderate disease, to decrease the incidence of side effects, the drug can be initiated at doses of 0.25-0.5 mg/kg, and then increased as tolerated to 0.5-1.5 mg/kg/day (**BIII**). Among patients with life-threatening disease, the target daily dose should be administered from the beginning (**BIII**). Following stabilization and resolution of fever, amphotericin B can be administered as 1.5 mg/kg body weight intravenously once every other day (**BIII**).
4. Duration of therapy in treatment of fungemia should be determined by the presence of deep tissue foci, patient clinical response, and presence of neutropenia. Patients at high risk for morbidity and mortality should be treated until all signs and symptoms of infection have resolved.
5. For candidemia, treatment is recommended until 2-3 weeks after the last positive blood culture and signs and symptoms have resolved (**AIII**). Among patients with persistent candidemia despite appropriate therapy, investigation for a deep tissue focus of infection should be conducted (e.g., echocardiogram, renal, or abdominal ultrasound).
6. Amphotericin undergoes renal excretion. Adverse effects of amphotericin B are primarily nephrotoxicity, defined by substantial azotemia from glomerular damage and can be accompanied by hypokalemia from tubular damage; nephrotoxicity is exacerbated by use of concomitant nephrotoxic drugs. Permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration with 0.9% saline intravenously over 30 minute before the amphotericin B infusion.
7. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than adults. Onset is usually within 1-3 hours after the infusion is started, typical duration is <1 hour, and the febrile reactions tend to decrease in frequency over time. Pretreatment with acetaminophen or diphenhydramine might alleviate febrile reactions. Idiosyncratic reactions including hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, and anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur.
8. Flucytosine (100-150 mg/kg/day divided into 4 doses) has been used in combination with amphotericin B in some patients with severe invasive candidiasis, particularly in patients with CNS disease (**CIII**). Flucytosine has the potential for considerable toxicity, especially affecting the bone marrow (e.g., anemia, leukopenia, thrombocytopenia), liver, gastrointestinal tract, kidney, and skin. Levels should be monitored and doses adjusted to keep the level between 40-60 micrograms/mL, particularly in patients with renal impairment where toxic levels can result in bone marrow suppression. The drug should be avoided in children with severe renal impairment (**EIII**).
9. Fluconazole has been used as alternative to amphotericin B for treatment of invasive disease in stable patients, such as those with uncomplicated

candidemia, who have not recently received azole therapy (**AI**). Higher doses of fluconazole are necessary for treatment of invasive fungal disease than those used for mucocutaneous or esophageal candidiasis. Alternatively, an initial course of amphotericin B therapy can be administered and then carefully followed by completion of a course of fluconazole therapy (**BIII**). However, fluconazole should not be initiated in the treatment of fungemia without knowing the speciation, because species such as *C. krusei* and *C. glabrata* are resistant to fluconazole (**EIII**).

10. Amphotericin B lipid formulations have a role among children who are intolerant of amphotericin B, have disseminated candidal infection that is refractory to conventional amphotericin B, or are at high risk for nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**BII**). Although lipid formulations appear to be at least as effective as conventional amphotericin B for treatment of serious fungal infections, the drugs are considerably more expensive than conventional amphotericin B. Three lipid formulations have been developed, including amphotericin B lipid complex (ABLC, Abelcet), liposomal amphotericin B lipid complex (AmBisome), and amphotericin B cholesteryl sulfate complex (ABCD). Experience with these preparations among pediatric patients is limited.
11. For invasive candidiasis, amphotericin B lipid complex (Abelcet) is administered as 5 mg/kg once daily given over 2 hours intravenously. Amphotericin B liposome (AmBisome) is administered as 3 to 5 mg/kg once daily over 1-2 hours intravenously. Duration of therapy is based on clinical response; most patients are treated for at least 2-4 weeks.
12. Acute, infusion-related reactions occur in approximately 20% of patients receiving lipid formulations, including chest pain, dyspnea, and hypoxia; severe abdomen, flank or leg pain; or flushing and urticaria. Compared with infusion reactions with conventional amphotericin B, most of the reactions to the lipid formulations (85%) occur within the first 5 minutes of infusion and rapidly resolve with temporary interruption of the amphotericin infusion and administration of intravenous diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

Cryptococcosis

Without treatment, cryptococcosis is fatal. Treatment for cryptococcal disease has not been studied in a controlled manner in pediatric patients. Data from the adult literature have resulted in a recommendation for the use of combination therapy for severe cryptococcosis and cryptococcal meningitis (**AI**). For children with severe disease that is isolated to the lungs, amphotericin B induction therapy, usually combined with an initial 2 weeks of flucytosine, is recommended until symptoms are controlled (**AI**). After treatment of acute pulmonary disease, maintenance therapy with fluconazole or itraconazole is recommended.

Adverse effects of amphotericin B are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration with 0.9% saline intravenously over 30 minute before the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than adults. Onset is usually within 1-3 hours after the infusion is started, typical duration is <1 hour, and the febrile reactions tend to decrease in frequency over time. Pretreatment with

acetaminophen or diphenhydramine might alleviate febrile reactions. Idiosyncratic reactions including hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, anemia, and neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also might occur.

Flucytosine has the potential for considerable toxicity, especially affecting the bone marrow (anemia, leukopenia, and thrombocytopenia), liver, gastrointestinal tract, kidney, and skin. Levels should be monitored and doses adjusted to keep the level between 40-60 micrograms/mL, particularly in patients with renal impairment where toxic levels can result in bone marrow suppression; the drug should be avoided among children with severe renal impairment (**EIII**).

For children with mild-to-moderate cryptococcosis that is isolated to the lungs, fluconazole alone can be used for treatment of HIV-infected children, followed by life-long suppressive therapy with fluconazole (**BII**). Alternatively, itraconazole can be used for treatment and suppressive therapy (**BII**). Fluconazole and the other azoles have relatively low rates of toxicity, but have substantial drug interactions that can limit their use. Because of their ability to inhibit the cytochrome P-450-dependent hepatic enzymes, the potential for drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy (**AIII**). Skin rash and pruritus might be seen with all azole drugs, and rare cases of Stevens-Johnson syndrome have been reported with fluconazole. Asymptomatic increases in transaminases and, less frequently, hepatitis can occur; rare cases of fatal hepatitis have been reported. Thrombocytopenia and leukopenia have been reported with itraconazole.

For meningeal and extrameningeal cryptococcosis, initial therapy with the combination of amphotericin B (at a dose of 0.7-1.5 mg/kg body weight/day) plus flucytosine (25 mg/kg/dose administered four times daily) for a minimum of 2 weeks (induction) is recommended (**AI**). This regimen was superior to single-drug therapy with either amphotericin B or fluconazole in two clinical trials among HIV-infected adults.

In cases of cryptococcal meningitis where flucytosine cannot be administered, amphotericin B alone can be administered (**BI**). Doses of 0.5-1.5 mg/kg/day of amphotericin B among children being treated for cryptococcal meningitis have been well tolerated. Lipid formulations of amphotericin B have been used for treatment of cryptococcal meningitis among adults and might be useful among patients with impaired renal function, although the optimal dose has not been determined; liposomal amphotericin B (AmBisome) at a dose of 4 mg/kg daily has been effective (**AI**). Children treated with liposomal amphotericin B (AmBisome) at a dose of 2 mg/kg/day have had a good effect, and doses to 7.5 mg/kg/day have been used for refractory cases. Acute, infusion-related reactions might be seen in about 20% of patients receiving lipid formulations, including chest pain, dyspnea, hypoxia, severe abdomen, flank or leg pain, and flushing and urticarial. The majority of reactions occurs within the first 5 minutes of infusion and rapidly resolves with temporary interruption of the amphotericin infusion and administration of intravenous diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

Fluconazole plus flucytosine is superior to fluconazole alone and provides an alternative option to amphotericin B for acute therapy of invasive disease; however, little data is available on this combination among children (**CIII**). The combination regimen has more toxicity than treatment with fluconazole alone.

After successful acute induction therapy in stable patients, amphotericin B and flucytosine can be discontinued and consolidation therapy with fluconazole (5-6 mg/kg/dose intravenously or orally administered twice daily) administered for a minimum of 8 weeks or until CSF cultures are stable (**AI**). Fluconazole has more rapid clearance and shorter half-life among children than adults, and higher doses of fluconazole are recommended for treatment of disseminated disease. Following induction and consolidation therapy, maintenance suppressive therapy with lower dose fluconazole should be instituted (**AI**). If fluconazole cannot be administered, itraconazole is an alternative for consolidation (2-5 mg/kg/dose administered twice daily), but might be less active than fluconazole (**BI**). In cases of refractory cryptococcal meningitis where systemic antifungal administration has failed, intrathecal or intraventricular amphotericin B has been used (**CII**).

Oral acetazolamide should not be used for reduction of elevated intracranial pressure in cryptococcal meningitis (**DIII**); it was associated with an excess of severe acidosis, hypokalemia, and other adverse effects compared with placebo in a clinical trial among adults. Recommendations for the management of elevated intracranial pressure are the same as for adults.

Prevention of relapse after successful treatment requires lifelong suppressive treatment; details on secondary prophylaxis (maintenance therapy) have been published. Safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART among children has not been studied extensively.

Histoplasmosis

Disseminated histoplasmosis is fatal without antifungal treatment. Treatment for disseminated histoplasmosis has not been studied in a controlled manner among pediatric patients. Pediatric treatment recommendations for HIV-infected children are based on data from the adult literature.

Among non-immunocompromised HIV-infected adults who do not require hospitalization and have mild symptoms of histoplasmosis, itraconazole alone has been used, administered for 3-4 months (**AII**). Although experience with itraconazole among children is limited, itraconazole capsules at doses of 6-8 mg/kg body weight/day given for 3-12 months has been used effectively for treatment of mild disseminated histoplasmosis in a limited number of non-immunocompromised children without HIV infection.

High-dose fluconazole is an alternative for patients with mild histoplasmosis who cannot take itraconazole, but is less effective, and the organism can develop drug resistance (**CII**). Because of the ability of the azole drugs to inhibit the cytochrome P-450-dependent hepatic enzymes, the potential for drug interactions should be carefully evaluated before initiation of therapy (**AIII**). For example, cardiac toxicity among patients receiving terfenadine or astemizole has been reported with concomitant itraconazole. The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting. Skin rash and

pruritus might be seen with azole drugs, and rare cases of Stevens-Johnson syndrome have been reported with fluconazole. Asymptomatic increases in transaminases might be observed in 1%-13% of patients receiving azole drugs, and less frequently, hepatitis; rare cases of fatal hepatitis have been reported. Thrombocytopenia and leukopenia have been reported with itraconazole.

Among HIV-infected adults or children with more severe disseminated histoplasmosis who require hospitalization or who are immunocompromised, amphotericin B is recommended for the initial phase of induction therapy (**AI**). Amphotericin B at a dose of 1 mg/kg for an average of 30 days has been effectively used for treatment of disseminated histoplasmosis in immunocompromised non-HIV-infected children. The duration of amphotericin B therapy among HIV-infected children is usually 4-6 weeks, followed by itraconazole chronic suppressive therapy.

Adverse effects of amphotericin B are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration with 0.9% saline intravenously over 30 minute before the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting might occur, although they are less frequent in children than adults. Onset is usually within 1-3 hours after the infusion is started, typical duration is <1 hour, and the febrile reactions tend to decrease in frequency over time. Pretreatment with acetaminophen or diphenhydramine can alleviate febrile reactions. Idiosyncratic reactions including hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, and anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures), also might occur.

Certain health-care providers limit amphotericin B therapy to 2-3 weeks, followed by 3-6 months of consolidation therapy with itraconazole after the patient is clinically stabilized and afebrile (**AII**). After successful treatment of acute disease, itraconazole chronic suppressive therapy (secondary prophylaxis) should be instituted. However, children with confirmed *H. capsulatum* meningitis, amphotericin B therapy should be continued for 12- 16 weeks, followed by chronic suppressive therapy (secondary prophylaxis) with itraconazole (**AII**).

Liposomal amphotericin B is an alternative for patients who cannot tolerate conventional amphotericin and in one randomized trial was associated with improved treatment response and survival and less toxicity compared with conventional amphotericin B induction therapy (**AI**). Acute, infusion-related reactions might be observed in approximately 20% of patients receiving lipid formulations, including chest pain, dyspnea, and hypoxia; severe abdomen, flank or leg pain; or flushing and urticarial. The majority of reactions occurs within the first 5 minutes of infusion and rapidly resolves with temporary interruption of the amphotericin infusion and administration of intravenous diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

Prevention of relapse after successful treatment requires lifelong suppressive treatment; details on secondary prophylaxis (maintenance therapy) have been published. Safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART among children has not been studies extensively.

Coccidioidomycosis

Experience is limited in treating coccidioidomycosis among HIV-infected children, and recommendations are generally based on experience with adults. On the basis of data from HIV-infected adults for treatment of diffuse pulmonary or disseminated disease, induction therapy with amphotericin B at a dose of 0.5-1.0 mg/kg body weight/day is recommended until clinical improvement is observed (**AII**); several weeks of therapy often are required to produce clear evidence of improvement. Following acute therapy, chronic suppressive therapy with fluconazole or itraconazole is recommended (**AII**).

Alternative treatment for disseminated nonmeningitic infection that is stable includes fluconazole (5-6 mg/kg administered twice daily) or itraconazole (4-10 mg/kg twice daily for 3 days followed by 2-5 mg/kg administered twice daily) (**BIII**).

CNS infections, including meningitis, should be treated with high-dose fluconazole (5-6 mg/kg/dose administered twice daily) because, unlike amphotericin B, it crosses the blood brain barrier well (**AII**). For CNS infections unresponsive to fluconazole, intravenous amphotericin B is used and augmented by intrathecal amphotericin B (**CI**). Consultation with a specialist is recommended when treating children with meningeal disease.

Fluconazole can inhibit the cytochrome P-450-dependent hepatic enzymes, and the potential for drug interactions should be evaluated carefully before initiation of therapy (**AIII**). The most frequent adverse effects of fluconazole are gastrointestinal, including nausea and vomiting. Skin rash and pruritus might be observed and rare cases of Stevens-Johnson syndrome have been reported with fluconazole. Asymptomatic increases in transaminases can be observed in 1%-13% of patients receiving azole drugs, and less frequently, patients with hepatitis; rare cases of fatal hepatitis have been reported.

Surgical debridement or excision of localized, persistent, progressive, or resistant lesions in bone and lung might be helpful. Lung cavities with recurrent bleeding and those larger than 6 cm in diameter are at greater risk for rupture and require surgery.

As with other disseminated fungal infections, continued chronic suppressive therapy with fluconazole or itraconazole is recommended following completion of initial therapy; details on secondary prophylaxis (maintenance therapy) have been published. Safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied exclusively.

Cytomegalovirus (CMV)

Treatment of newborns with symptomatic congenital CMV disease with ganciclovir (4-6 mg/kg administered intravenously every 12 hours for 6 weeks) has been evaluated in a phase II study. The higher dose of 12 mg/kg body weight/day led to a substantial decrease in the overall quantity of virus in the urine and other sites (**BI**). In a phase III trial of ganciclovir treatment of infants with symptomatic congenital CMV infection, ganciclovir begun in the neonatal period resulted in more rapid resolution of liver enzyme abnormalities and less hearing loss at age

6-12 months compared with no treatment, although approximately two thirds of the infants had substantial neutropenia during therapy. Neutropenia was severe enough to require dose modification in 48% and treatment with granulocyte colony stimulating factor in 7% and was complicated by gram-negative sepsis in one neonate.

The drug of choice for initial treatment of disseminated CMV disease, including CMV retinitis, in HIV-infected children is intravenous ganciclovir (**AI**). The dose is 5 mg/kg/dose twice daily administered intravenously over 1-2 hours for 14-21 days followed by lifelong maintenance therapy. With long-term therapy, the emergence of ganciclovir-resistant CMV strains has occurred. The major side effect of ganciclovir is myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia). Dose reduction or interruption might be necessary in up to 40% of patients because of hematologic toxicity; granulocyte colony-stimulating factor can be used to ameliorate marrow suppression. Renal toxicity, as seen by increased serum creatinine, also can occur and might require ganciclovir dose modification. Other toxic reactions include CNS effects, gastrointestinal dysfunction, thrombophlebitis, and elevated liver enzymes.

An alternative drug to treat CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children is foscarnet (**AI**). Foscarnet when used for suppression has been associated with increased length of survival relative to ganciclovir in HIV-infected adult patients. The pediatric dose is 60 mg/kg/dose every 8 hours administered intravenously over 1-2 hours for 14-21 days followed by lifelong maintenance therapy. The dose of foscarnet should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/minute). Infusing foscarnet with saline fluid loading can minimize renal toxicity. Doses should be modified among patients with renal insufficiency. The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions such as calcium leads to metabolic abnormalities in approximately one third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur.

Combination therapy with ganciclovir and foscarnet delays progression of retinitis in certain patients failing monotherapy and can be used as initial therapy among children with sight-threatening disease (**BIII**). Combination therapy also has been used for adult patients with retinitis that has relapsed on single-agent therapy.

Valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis at an induction dose of 900 mg orally twice daily for 21 days, followed by 900 mg orally once daily as maintenance (**AI**). Valganciclovir is well absorbed from the gastrointestinal tract and rapidly metabolized to ganciclovir in the intestine and liver. Its major adverse effect is myelosuppression. However, data on appropriate dosage of this drug for children are not available (**CIII**).

Before the availability of valganciclovir, oral ganciclovir in combination with an intraocular ganciclovir implant had been used for maintenance treatment of CMV retinitis in adults. Oral ganciclovir has been studied in a limited number of children. Children require a higher oral dose of ganciclovir than adults to achieve

target serum levels because of low bioavailability and greater clearance. A dose of 30 mg/kg administered orally every 8 hours produced serum levels similar to the dose effective for maintenance treatment of CMV retinitis in adults (1 g orally every 8 hours). The combination of oral ganciclovir with a ganciclovir sustained release intraocular implant, replaced every 6-9 months, could be considered for treatment and chronic suppression of CMV retinitis in older children (**BIII**). Among children old enough to receive the adult dosage, valganciclovir would be the preferred drug instead of oral ganciclovir (**AI**).

Cidofovir (5 mg/kg intravenously once a week for 2 weeks, then 5 mg/kg once every 2 weeks for maintenance therapy) is effective in treating CMV retinitis among adult patients who are intolerant of other therapies (**AI**). However, cidofovir has not been studied in pediatric patients with CMV disease (**CIII**). The major side effect of cidofovir is nephrotoxicity; the drug produces proximal tubular dysfunction including Fanconi syndrome and acute renal failure. To minimize nephrotoxicity, probenecid should be administered before each infusion, and intravenous hydration with normal saline should be administered before and after each cidofovir infusion; renal function should be carefully monitored. Neutropenia also has been reported. Other reported adverse effects include anterior uveitis and ocular hypotony; ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug.

Intravitreous injections of ganciclovir, foscarnet, or cidofovir have been used for control of retinitis but require biweekly intraocular injections. Data are limited in children, and biweekly injection is impractical for use in most children (**DIII**). Implantation of an intravitreous ganciclovir medication release device in the posterior camber of the eye also has been used in HIV-infected adults and adolescents. Intraocular implants should not be used in children aged <3 years because of the small size of the eyes in young children (**EIII**).

Fomivirsen (Vitravene) is an antisense nucleotide that binds to CMV messenger ribonucleic acid (mRNA), has potent anti-CMV activity, and is available as an aqueous solution for intravitreous injection. The drug has been studied in a controlled trial in HIV-infected adults and is approved for intraocular use in adults with AIDS who have persistent active CMV retinitis despite other anti-CMV therapies or who cannot tolerate other treatments (**AI**); no studies have been conducted among pediatric patients (**CIII**). Complications of intraocular therapy include vitreous hemorrhage, retinal detachment, and endophthalmitis. Intraocular maintenance therapy does not prevent extension to the opposite eye or development of systemic disease and therefore, when used, should be combined with oral ganciclovir or oral valganciclovir to provide systemic therapy.

Among HIV-infected children with CMV disease, after initial induction therapy, lifetime chronic suppressive maintenance therapy for CMV (secondary prophylaxis) is required; detailed recommendations have been published. Safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

Herpes simplex Virus (HSV)

Acyclovir is the drug of choice for treatment of HSV among infants and children, regardless of HIV-infection status. Both oral and intravenous preparations are

available. Neonatal HSV disease should be treated with high-dose intravenous acyclovir (20 mg/kg body weight/dose three times daily) administered for 21 days for CNS and disseminated disease and for 14 days for skin, eye, and mouth disease (**AI**). Acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA polymerase chain reaction (PCR) assay is negative at day 19-21 of treatment (**BIII**). Although treatment has reduced morbidity and mortality, infants with neonatal HSV infection remain at risk for neurologic sequelae, with the most severe neurologic sequelae seen in those with CNS disease. A limited percentage (2%-6%) of infants with localized skin, eye, or mucus membrane disease might have later neurologic sequelae after apparently successful treatment.

Disseminated HSV disease or encephalitis outside of the neonatal period should be treated with intravenous acyclovir with a dose of 10 mg/kg/dose or 500 mg/m^2/dose three times daily for 21 days (**AII**). HIV-infected children with symptomatic HSV gingivostomatitis should be treated with intravenous acyclovir (5-10 mg/kg/dose three times daily) or oral acyclovir (20 mg/kg/dose three times daily) for 7-14 days (**AII**). HIV-infected children who have severe oral HSV recurrences (more than 3-6 severe episodes a year) can be considered for secondary suppressive therapy with oral acyclovir (**AI**).

Acyclovir is primarily excreted by the kidney; as a result, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure. Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. In infants receiving high-dose acyclovir for neonatal disease, the major toxicity was neutropenia (absolute neutrophil count $<1,000/mm^3$). Grade 3 or higher nephrotoxicity was observed in 6%.

Pediatric experience with the oral preparation of acyclovir is limited for children aged <2 years. Among infants who received long-term oral acyclovir suppressive therapy (300 mg/m^2 body surface area/dose given 2-3 times daily) following treatment for neonatal HSV infection, a relatively high rate of neutropenia (46%) was observed, although in most cases this was self-limited and did not require dose modification or drug discontinuation.

Among HIV-infected children with acyclovir-resistant HSV infection, intravenous foscarnet is recommended at a dose of 120 mg/kg/day in 2-3 divided doses administered intravenously over 1-2 hours until the infection resolves (**AI**). The dose of foscarnet should be administered slowly over the course of 2 hours (or no faster than 1 mg/kg/minute). Infusing foscarnet with saline fluid loading can minimize renal toxicity. Doses should be modified in patients with renal insufficiency. The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions such as calcium leads to metabolic abnormalities in approximately one third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms also can occur.

Valacyclovir is a prodrug of acyclovir with improved bioavailability; bioavailability is 50%-55% in adults (3-5 times higher than that of oral acyclovir). Valacyclovir is rapidly converted to acyclovir after absorption and is not active against acyclovir-

resistant HSV strains. It is approved for use in adults and adolescents for treatment of genital herpes at a dose of 1 g twice daily for 7-10 days (**AII**). Dose adjustment (based on creatinine clearance) is needed among patients receiving valacyclovir who have renal insufficiency or renal failure. Data are limited on valacyclovir in children (**CIII**). In a study of valacyclovir among children with leukemia, bioavailability of acyclovir was 45% after a median oral dose of 34.1 mg/kg of valacyclovir. In a second study in 28 immunocompromised children aged 5-12 years, children were randomized to receive 250 mg (9.4-13.3 mg/kg) or 500 mg (13.9-27.0 mg/kg) valacyclovir twice daily; the overall estimated acyclovir bioavailability was 48%. An oral dose of valacyclovir of 30 mg/kg/dose administered three times a day to a child with normal renal function was estimated to provide acyclovir concentrations similar to those achieved with standard acyclovir dosing of 10 mg/kg/dose intravenously three times daily. Valacyclovir is available only in caplet formulation, but a suspension formulation can be prepared in Ora-Sweet® or Syrpalta® syrups (to yield a final concentration of 50 mg/mL of the hydrochloride salt) that is stable for 21 days if stored in amber glass bottles.

Adverse effects of valacyclovir are similar to acyclovir; nausea and vomiting are most common. Thrombotic microangiopathy (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) has been reported in HIV-infected adults with advanced disease who received high-dose valacyclovir (8 grams per day). However, it was not reported in other studies in which valacyclovir was administered in lower doses (250 mg-1,000 mg/day).

Penciclovir is an acyclic guanine analog derivative with similar activity and mechanism of action as acyclovir, although penciclovir has a longer intracellular half-life. It is not active against acyclovir-resistant HSV strains. It has poor bioavailability and is only available as a 1% cream for topical application. It is approved for treatment of recurrent herpes labialis in immunocompetent adults (applied every 2 hours while awake). No data are available about use of penciclovir treatment in children.

Famciclovir is the oral prodrug of penciclovir; its bioavailability is approximately 75% compared with 5% for penciclovir. It is approved for treatment of recurrent mucocutaneous HSV infection in HIV-infected adults and adolescents at a dose of 500 mg orally twice daily for 7 days (**AII**). Famciclovir is available only in tablet form, and no specific data on children are available (**CIII**). Dose adjustment (based on creatinine clearance) is needed among patients with renal insufficiency or renal failure. Adverse effects are rare; these include gastrointestinal disturbances, rash, and CNS complaints (e.g., confusion, hallucinations and disorientation), neutropenia, and elevated liver transaminases.

Varicella-Zoster Virus (VZV)

On the basis of controlled trials among children with malignancies, acyclovir is the drug of choice for treatment of VZV infection among HIV-infected children (**AI**). With primary varicella, acyclovir should be initiated as soon as possible after initial lesions appear. New lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all lesions might take 5-7 days.

Intravenous acyclovir is recommended for treatment of primary varicella among HIV-infected children with moderate or severe immunosuppression or who have high fever or numerous or deep, necrotic, or hemorrhagic skin lesions (**AIII**). For children aged <1 year, the dose of acyclovir is 10 mg/kg body weight/dose administered intravenously every 8 hours as a 1-hour infusion. Some health-care providers administer the same dose for children aged ≥1 year, and others use acyclovir based on body surface area among children aged ≥1 year old (500 mg/m^2/dose intravenously every 8 hours as a 1-hour infusion). Administration is for 7 days or until no new lesions have appeared for 48 hours. Oral administration should be used only for treatment of primary varicella among HIV-infected children with normal or only slightly decreased CD4+ cell counts or in children with mild disease (**BIII**). The dose is 20 mg/kg per dose administered orally 4 times daily (maximum dose: 800 mg).

Acyclovir is the treatment of choice for zoster among HIV-infected children (**AII**). With zoster, oral acyclovir can be administered because the chance for disseminated, life-threatening disease is less with zoster than varicella. Initial intravenous administration should be considered for HIV-infected children with severe immunosuppression, trigeminal nerve involvement, or extensive multidermatomal zoster (**AII**).

Acyclovir is primarily excreted by the kidney, and dose adjustment (based on creatinine clearance) is needed among patients with renal insufficiency or renal failure. Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. Among infants receiving high-dose acyclovir for neonatal HSV disease, the major toxicity was neutropenia (absolute neutrophil count $<1,000/mm^3$), which was observed in 21% of children. Grade 3 or higher nephrotoxicity was observed in 6% of children.

Pediatric experience with the oral preparation of acyclovir is limited in children aged <2 years. In infants who received long-term oral acyclovir suppressive therapy (300 mg/m^2 body surface area/dose administered 2-3 times daily) following treatment for neonatal HSV infection, a relatively high rate of neutropenia (46%) was observed, although in the majority of cases this was self-limited and did not require dose modification or drug discontinuation.

Children who continue to develop lesions or whose lesions fail to heal might be infected with acyclovir-resistant VZV. HIV-infected children with acyclovir-resistant VZV can be treated with intravenous foscarnet (**BII**). The dose is 40-60 mg/kg per dose 3 times daily administered intravenously over 1-2 hours for 7 days or until no new lesions have appeared for 48 hours. The dose of foscarnet should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/minute). Infusing foscarnet with saline fluid loading can minimize renal toxicity. Doses should be modified among patients with renal insufficiency.

The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions (e.g., calcium) leads to metabolic abnormalities in approximately one third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur.

Valacyclovir is a prodrug of acyclovir with improved bioavailability. It is not active against acyclovir-resistant VZV strains. It is approved for treatment of zoster among adults at a dose of 1,000 mg given orally 3 times a day for 7 days (**AII**). However, data are limited for its use in children (**CIII**). Valacyclovir is available only in caplet formulation, but a liquid formulation that is stable for 21 days can be prepared in Ora-Sweet® and Syrpalta® syrups and stored in amber glass bottles.

Adverse effects of valacyclovir are similar to those with acyclovir; nausea and vomiting are most common. Thrombotic microangiopathy (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) has been reported among HIV-infected adults with advanced disease who received high-dose valacyclovir (8 g/day). However, this condition has not been reported in other studies in which valacyclovir was administered in lower doses (250-1,000 mg/day).

Famciclovir is the oral prodrug of penciclovir. It is not active against acyclovir-resistant VZV strains. Famciclovir is approved for the treatment of zoster in immunocompetent adults in a dose of 500 mg orally every 8 hours for 7 days (**AII**). It is comparable in efficacy to oral acyclovir in treatment of immunocompromised adults with localized zoster, although it has not been approved for this indication. It is available only in tablet form. No specific data about dosing information in children are available, although immunocompromised persons aged 12-18 years were included in a study of famciclovir for localized zoster (**CIII**).

Human Papillomavirus (HPV)

Multiple treatments for HPV-associated skin and external genital lesions exist; however, no single treatment is ideal for all patients or all lesions (**CIII**). Standard topical therapy for HPV-associated lesions among HIV-infected children is often ineffective. Treatment can induce wart-free periods, but the underlying viral infection can persist and result in recurrence. In addition, topical treatments are seldom effective in patients with large or extensive lesions. However, individual lesions can be destroyed using cryotherapy or electrodessication.

Topical treatments include podofilox solution and gel (0.5%) (antimitotic agent), imiquimod cream (5%) (topical immune enhancer that stimulates production of interferon and other cytokines), trichloroacetic or bichloroacetic acid 80%-95% aqueous solution (caustic agents that destroy warts by chemical coagulation of proteins), and podophyllin resin (contains antimitotic compounds and mutagens)**.** Podofilox is applied to all lesions twice a day for 3 consecutive days and can be repeated weekly up to 4 weeks (**BIII**). Imiquimod is applied at bedtime and removed with water the following morning (**BII**). It should be applied 3 nonconsecutive nights a week for up to 16 weeks**.** HIV-infected patients with immunosuppression might have a lower response rate to imiquimod.

Acid cauterization and podophyllin resin require application by a health-care provider. Acid cauterization should be discontinued if substantial improvement is not observed after three treatment sessions or complete clearance has not occurred after six treatments (**BIII**). Podophyllin resin is applied and removed by washing a few hours later; applications can be repeated weekly for up to 6 weeks (**CIII**). Systemic absorption can occur if applied to a large area, causing nausea,

vomiting, or CNS effects. Efficacy of the various topical agents in patients without HIV infection ranges from 20%80%. Major toxicity of topical agents is local pain or irritation of adjacent normal skin.

Cidofovir topical gel (1%) is an experimental topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection in a placebo-controlled trial; a complete response was observed in 47% of cidofovir recipients compared with none in the placebo group (**CIII**). Successful use of cidofovir gel for treatment of severe molluscum contagiosum in children with HIV infection and congenital primary immunodeficiency has been reported. Topical cidofovir might have certain systemic absorption and be associated with renal toxicity.

Individual lesions can be removed by using cryotherapy or electrodessication (**BIII**). Cryotherapy (application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1-2 weeks up to four times. The major toxicity is local pain. Curettage, electrosurgery, scissor excision, or laser vaporization also can be effective. Injectable therapy (e.g., interferon or 5-fluorouracil/epinephringel implant) has been used.

Laryngeal papillomatosis is difficult to manage. Treatment is directed toward removing lesions obstructing the airway rather than at the elimination of disease. Lesions are removed by debridement or laser. Systemic interferon-alfa therapy or intralesional cidofovir has been used as an investigational treatment in children with frequent recurrences or extension into the trachea, bronchi, or lung parenchyma (**CIII**).

Management of anogenital HPV infection accompanied by cytologic changes indicating dysplasia/carcinoma among children/adolescents is analogous to that for the adult population. HAART has not been consistently associated with a reduced risk for HPV-related cervical abnormalities in HIV-infected women. However, an "immune reconstitution"-like syndrome related to the occurrence of HPV-associated oral warts among HIV-infected adults has been observed in which the occurrence of oral warts was associated with a decrease in HIV ribonucleic acid (RNA) levels with highly active antiretroviral therapy. Immune reconstitution in response to viral load reduction might result in a return of marked inflammatory responses against latent oral HPV infection.

Hepatitis C

Hepatitis A vaccine should be administered to susceptible children aged $\geq$2 years with chronic viral hepatitis (**AIII**). Children with symptomatic chronic hepatitis C or histologically advanced pathologic features (bridging necrosis or active cirrhosis) should be considered for treatment (**BI**). Patients infected with hepatitis C virus (HCV) genotype 1 have a less favorable response to therapy than those infected with HCV genotypes 2 or 3. In an analysis of published trials, sustained clearance of HCV RNA with interferon monotherapy was 26% in patients with HCV genotype 1 infection compared with 70% in patients with HCV genotype 2 or 3 infections.

Quantitative HCV RNA levels are used to assess treatment response; a sustained virologic response is defined as absence of detectable HCV RNA at the end of

treatment. In adults with chronic hepatitis C, HCV RNA levels usually are assessed at baseline (i.e., before therapy) and after 12 and 24 weeks of therapy. Persons with undetectable HCV RNA at completion of therapy should be retested 24 weeks after completion of therapy. In HIV-coinfected patients, certain health-care providers continue to do serial HCV RNA testing at 6-month intervals for an additional 1-2 years to exclude later virologic relapse.

Among adults with HCV disease, regardless of HIV infection status, combination therapy (interferon plus ribavirin) is the preferred initial therapy because of substantially higher rates of virologic response than with interferon monotherapy (**AI**). On the basis of data from adults, treatment recommendations for children with HCV disease are similar (**AI**).

Pegylated interferon-alfa requires once weekly administration and results in more sustained interferon blood levels than with standard interferon. Adult studies have demonstrated increased efficacy with once weekly subcutaneous administration of pegylated interferon-alfa-2B plus ribavirin compared with standard interferon-alfa-2b plus ribavirin. The combination of pegylated interferon-alfa-2b (1.5 micrograms/kg body weight) or -2a (180 micrograms) administered subcutaneously once weekly plus ribavirin (400 mg orally administered twice daily) is the preferred initial therapy for adults with HCV infection (**AI**). Adults with contraindications to the use of ribavirin have been treated with pegylated interferon monotherapy, although the response rate is decreased (**AII**). However, data on the safety and dosing of pegylated interferon-alfa for children are not available (**CIII**).

Interferon-alfa-2a or -2b monotherapy is the therapy that has received the most study among HCV-infected children; none of the studies specifically evaluated therapeutic response to interferon among children coinfected with HIV and HCV. In a review of 20 published studies of interferon-alfa monotherapy in HCV-infected pediatric patients without HIV infection, the average end-of-treatment response (negative HCV RNA polymerase chain reaction [PCR]) rate was 54% (range: 0-91%) and the sustained response rate was 36% (range: 0-73%). The youngest child treated in these studies was aged 2 years. Doses of interferon-alfa used in the pediatric studies have ranged from 1.75 to 5 million units (MU)/m^2 (maximum dose: 3-5 MU) administered subcutaneously or intramuscularly three times weekly for 4-12 months. In one study, an induction dose of 0.1 MU/kg (maximum dose: 6 MU) was administered subcutaneously once daily for 2 weeks, followed by the same dose administered three times weekly for 22 additional weeks. In another study, treatment was initiated at 25%-50% of the final dose and advanced to the final dose over the first 1-1 1/2 weeks. A commonly used regimen in children is 3-5 MU/m^2 given subcutaneously three times a week (**BII**). Treatment with interferon-alfa-based therapies is contraindicated in children with decompensated liver disease, significant cytopenias, severe renal or cardiac disorders, and autoimmune disease (**EII**).

Ribavirin oral solution has been approved for treatment of chronic hepatitis C among children aged >3 years with compensated liver disease and for use in combination with interferon alfa-2b, primarily based on data in adults (**AII**). The dose of interferon-alfa-2b is 3-5 MU/m^2 administered subcutaneously three times a week. Administration of ribavirin in a fixed dose by weight is recommended. Interferon-alfa monotherapy can be used among children with contraindications to

ribavirin who cannot receive combination therapy (e.g., unstable cardiopulmonary disease, severe pre-existing anemia, or hemoglobinopathy) (**BII**).

The ideal length of treatment for HIV-HCV coinfected children is unknown. On the basis of recommendations in HIV-uninfected adults, the duration of treatment using interferon-ribavirin combination therapy 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 can have treatment discontinued after 12 weeks because they have a limited chance of achieving a sustained virologic response, regardless of duration of therapy, and toxicity outweighs any potential benefit (**BI**). For patients who are not coinfected with HIV who have HCV genotype 2 or 3 disease, the recommended treatment duration is 24 weeks (**BII**). However, some health-care providers would treat HIV-HCV-coinfected person with HCV genotype 2 or 3 disease with 48 weeks of combination therapy (**CIII**).

Adverse effects of interferon-alfa in children, although frequent, are usually not severe; only 5% of children require treatment discontinuation. Toxicity is dose-related, with a higher rate of side effects with doses of 10 MU/m^2. The incidence of the majority of adverse effects decreases substantially during the first 4 months of therapy. Premedication with acetaminophen might reduce the incidence of side effects (**BIII**). The most common adverse effect of interferon-alfa is an influenza-like syndrome that can consist of fever, chills, headache, myalgia, and arthralgia, abdominal pain, nausea, and vomiting. Fever appears within 2-6 hours after interferon injection, and febrile seizures have occurred; influenza-like symptoms are most severe during the first month of treatment. Relapsing cases of epistaxis not associated with thrombocytopenia or prolonged prothrombin time have been reported among certain children and occurred more frequently in the first months of treatment. Certain children experience loss of appetite and a transient weight loss and impairment in height growth, which resolves after completion of therapy. Transient mild alopecia, usually first occurring after 2-3 months of therapy, also has been reported. Subtle personality changes have been reported in 42% of children; they resolve when therapy is discontinued. Neutropenia, which resolves upon discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Certain children have experienced antinuclear autoantibodies.

Periodic monitoring of a complete blood count is recommended among children receiving interferon-alfa therapy. Abnormalities in thyroid function (hypo- or hyperthyroidism) have been reported with interferon-alfa therapy; periodic monitoring of thyroid stimulating hormone (TSH) is recommended.

Interferon should be permanently discontinued if a life-threatening toxicity occurs (**AII**). For severe but non-life-threatening reactions, the drug can be temporarily discontinued and reinstated when the reaction has resolved in a stepwise fashion beginning with a maximum of 50% of the last administered dose; for moderate reactions, the dose can be reduced by 50% and then increased stepwise by 0.5 or 1 MU/m^2 up to the full dose after the adverse effect has resolved (**BIII**).

Side effects of ribavirin include those observed with interferon alone (e.g., influenza-like syndrome and neutropenia); adverse effects more specific to

ribavirin include hemolytic anemia and lymphopenia. Depression and suicidal ideation have also been observed with this combination. The hemolytic anemia that occurs with the use of ribavirin is dose-dependent, might cause a substantial decrease in hemoglobin, and usually occurs within 1-2 weeks of therapy initiation. Therefore, hemoglobin or hematocrit should be obtained pretreatment and at week 2 and week 4 of therapy, or more frequently if clinically indicated.

Ribavirin inhibits intracellular phosphorylation of pyrimidine nucleoside analogues (zidovudine, stavudine, zalcitabine) in vitro, but the clinical significance of this interaction in vivo is unclear. Ribavirin enhances intracellular phosphorylation of didanosine; case reports have indicated a potential increased risk for pancreatitis and mitochondrial toxicity with concomitant use, and this combination should be used with caution.

Hepatitis B

Hepatitis A vaccine should be administered to susceptible children aged $\geq$2 years with chronic viral hepatitis (**AIII**). Early treatment, if started before integration of viral DNA in the majority of host hepatocytes nuclear DNA, might provide improved long-term outcome; however, whether treatment of acute hepatitis B virus (HBV) infection offers additional benefit over treatment after infection is known to be chronic is not known and requires further study.

Indications for treatment of chronic HBV infection in HIV-coinfected children are the same as in HBV-infected children without HIV infection and include 1) evidence of ongoing viral replication, as indicated by the presence of detectable serum HBV DNA, with or without hepatitis B e antigen (HBeAg) positivity, for at least 6 months; 2) persistent elevation of serum transaminases (at least twice the upper limit of normal); and 3) evidence of chronic hepatitis on liver biopsy (**BII**). Patients without necroinflammation usually do not warrant antiviral therapy.

The correlates of successful therapy are not well defined, but markers of improvement would include improved liver histology on biopsy, normalization of hepatic transaminases, substantial decrease in HBV viral load (HBV DNA levels), and loss of e antigen with development of e antibody in patients who are HBeAg positive. Although a decline in viral load correlates with response, no target HBV DNA level has been established as representing a successful virologic response. Monitoring for virologic response of therapy should include regular determination of serum levels of HBV DNA, hepatitis B surface antigen (HBsAg), HBeAg, anti-HBe antibody, and serum transaminases (**AIII**).

Three therapies have been approved for chronic hepatitis B in adults: interferon-alfa, lamivudine (3TC), and adefovir. Interferon-alfa and 3TC are also approved for treatment of chronic hepatitis B in children. For treatment of chronic hepatitis B in HIV-HBV coinfected adults, some specialists recommend that interferon-alfa is the therapy of choice in persons who do not yet require antiretroviral therapy for HIV infection to preserve use of 3TC and tenofovir for later treatment of HIV infection (**CIII**). For HIV-HBV coinfected adults who are antiretroviral-naive and require both HBV and HIV treatment, 3TC is considered by some specialists to be the therapy of choice for HBV, administered in HIV-suppressive doses and in combination with other antiretroviral drugs for treatment of HIV infection (**BIII**). Considerations would be similar for HIV-HBV coinfected children.

Interferon-alfa-2a or -2b is the therapy that has received the most study in HBV-infected children and is recommended for the treatment of chronic hepatitis B with compensated liver disease in patients aged $\geq$2 years who warrant treatment (**BII**). Interferon-alfa therapy is contraindicated for children with decompensated liver disease, substantial cytopenias, severe renal or cardiac disorders, and autoimmune disease (**EII**).

None of the clinical studies of interferon-alfa therapy of chronic hepatitis B have specifically studied children with HIV-HBV coinfection. Certain studies of interferon-alfa therapy in HBV-HIV coinfected adults indicate that response to therapy might be less than in adults not infected by HIV.

In a review of six randomized clinical trials in 240 HBV-infected children aged >1.5 years, interferon-alfa therapy resulted in HBV DNA clearance in 35% of treated children, HBeAg clearance in 10%, and normalization of serum transaminases in 39% at the end of therapy. Six to 18 months after therapy discontinuation, 29% of children had persistent HBV DNA clearance, and 23% HBeAg clearance. Interferon alfa-2a or -2b doses ranged from 3 MU/m^2 to 10 MU/m^2 administered subcutaneously three times weekly for 3-12 months. A commonly used regimen in children is 5 MU/m^2 three times weekly for 6 months (**BII**). In adults with chronic hepatitis who are HBeAg-negative, longer therapy (minimum: 12 months) is recommended because response to interferon therapy is lower than in HBeAg-positive patients (**BIII**).

More prolonged interferon-alfa therapy is associated with better virologic response in children. Long-term response is also better in children with higher (approximately twice the upper limit of normal) serum transaminase levels and lower HBV DNA at baseline. Studies have indicated improved virologic response with higher dose (i.e., 10 MU/m^2 three times weekly) interferon therapy as initial therapy or for retreatment of children who have failed before lower dose interferon therapy (**CII**). Data from pediatric trials that initiated interferon therapy with prednisone priming had results comparable to those observed with interferon alone; therefore, prednisone administration is not recommended (**DII**).

Adverse effects of interferon-alfa in children, while frequent, are usually not severe; approximately 5% of children require treatment discontinuation. Toxicity is dose-related with a higher rate of side effects with doses of 10 MU/m^2. Incidence of the majority of adverse effects decreases substantially during the first 4 months of therapy. Premedication with acetaminophen might reduce the incidence of side effects (**BIII**).

The most common adverse effect of interferon-alfa is an influenza-like syndrome that can consist of fever, chills, headache, myalgia, arthralgia, abdominal pain, nausea, and vomiting. Fever usually appears within 2-6 hours after interferon injection, and rarely febrile seizures have occurred; the influenza-like symptoms are most severe during the first month of treatment. Relapsing cases of epistaxis (not associated with thrombocytopenia or prolonged prothrombin time) have been reported in certain children and occurred more frequently in the first months of treatment. Certain children experience loss of appetite and a transient weight loss and impairment in height growth, which resolves after completion of therapy. Transient mild alopecia, usually first occurring after 2-3 months of therapy, also has been reported. Subtle personality changes have been reported in 42% of

children that resolve when therapy is discontinued. Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Certain children have experienced antinuclear autoantibodies. Periodic monitoring of a complete blood count is recommended in children receiving interferon-alfa therapy.

Abnormalities in thyroid function (hypo- or hyperthyroidism) have been reported with interferon-alfa therapy; periodic monitoring of thyroid stimulating hormone (TSH) is recommended. Interferon should be permanently discontinued if a life-threatening toxicity occurs (**AII**). For severe but non-life-threatening reactions, the drug can be temporarily discontinued, and after the reaction has resolved, treatment can be reinstated in a stepwise fashion, beginning with a maximum of 50% of the last administered dose. For moderate reactions, the dose can be reduced by 50% and then increased stepwise by 0.5 or 1 MU/m^2 up to the full dose after the adverse effect has resolved (**BIII**).

Pegylated interferon alfa, which can be administered once weekly, is being studied in adults with HIV-HBV coinfection. The drug has been studied in a limited number of HIV-infected children for treatment of HIV, but data are not yet available (**CIII**).

For children who have not responded to interferon-alfa, treatment with interferon-beta (5 MU/m^2 intramuscularly three times a week for 6 months), which shares common biologic functions with interferon-alfa but is antigenically different, can be considered (**CIII**). In a limited number of children, therapy was well tolerated with a low-grade fever the most common side effect. At 18 months after completion of therapy, 45% of children were HBV DNA negative, 32% became anti-HBe antibody positive, and 50% normalized serum transaminase levels. Liver histopathology had substantial improvement in those children who responded to therapy.

3TC is approved for children and adults for the treatment of compensated chronic hepatitis B associated with evidence of HBV replication and active liver inflammation and would be the preferred therapy (as part of a fully suppressive HAART regimen) for chronic hepatitis B in HIV-infected children who require HIV therapy (**BIII**). 3TC treatment results in a rapid decline in HBV DNA levels and is well tolerated in HBV-infected children who are not HIV-infected, although persistent virologic response rates with 3TC monotherapy are low. In a study of children with HBV infection who were not HIV coinfected, 23% of 191 children who received 52 weeks of treatment with 3TC had a virologic response (i.e., the absence of HBe antigen and serum HBV DNA) compared with 13% of 91 who received placebo. 3TC has been used both as primary therapy and as secondary therapy for children without HIV infection who have not responded to interferon-alfa treatment. Reports of clinical and laboratory exacerbations of hepatitis after discontinuation of 3TC treatment have occurred among children with HBV infection who are not infected with HIV. The optimal duration of therapy is not known.

Extended treatment with 3TC can lead to the development of 3TC-resistant HBV, with base pair substitutions at the YMDD locus of DNA polymerase. In one pediatric study, 19% of HBV-infected patients treated with 3TC for 1 year had emergence of the YMDD HBV-variant; a more recent study reported mutant

variants in 65% of 3TC treated children unresponsive to interferon, compared with 16%-32% in HBV-infected adults treated with 3TC for 1 year, and 49% after 3 years. However, the emergence of variants containing the YMDD motif mutation did not prevent HBeAg seroconversion or result in substantial worsening of liver histology. 3TC resistance should be suspected if HBV replication (as measured by HBV DNA levels) increases or recurs while receiving treatment.

Among children with HIV-HBV coinfection, 3TC should not be administered as monotherapy because resistance of HIV to 3TC develops (**EI**). The dose of 3TC approved to treat HBV infection (3 mg/kg body weight once daily) is lower than that required to treat HIV (4 mg/kg twice daily, maximum dose 150 mg twice daily). If 3TC is administered to HIV-HBV coinfected children at the lower dose, the resulting subtherapeutic blood levels of 3TC will result in the development of 3TC-resistant HIV; emergence of the M184V 3TC resistance mutation is observed after only 1-2 weeks of single drug therapy. In contrast, the dose of 3TC used to treat HIV as part of combination antiretroviral therapy is adequate to treat HBV. Thus, among HIV-HBV coinfected children, if 3TC is used to treat chronic hepatitis B, 3TC should be administered at the dose of 4 mg/kg twice daily in the context of a potent combination antiretroviral regimen (**BIII**).

To reduce the development of resistance, some specialists in adult HIV infection recommend use of adefovir or tenofovir in addition to 3TC as part of a fully suppressive HAART regimen among HIV-infected adults who require treatment for both HIV and chronic hepatitis B, although data to support this approach are limited (**CIII**). No data are available on appropriate dosing and safety of adefovir or tenofovir in children.

Because clinical and laboratory exacerbations of hepatitis might occur if 3TC is discontinued among children who are responding to therapy, after anti-HBV-HIV therapy has begun, it should be continued unless contraindicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation (**BIII**). If 3TC is discontinued, careful monitoring of serum transaminases and HBV DNA is important.

Combination with 3TC and interferon-alfa has not been demonstrated to be more effective than treatment with interferon alone in adult patients. Combined treatment with 3TC and interferon-alfa (10 MU/m^2 administered subcutaneously three times weekly) administered for 6 to 12 months has been studied in 57 HBV-infected children aged >2 years. Sustained complete responses (clearance of HBeAg, HBeAb seroconversion, and normalization of serum transaminases) was observed 6 months after completion of therapy in 20% of those receiving 6 months and 37% of those receiving 12 months of therapy. However, use of this combination in pediatric patients is not recommended until more data are available (**DII**).

Adefovir dipivoxil (10 mg once daily) is a nucleotide analogue drug active against HBV. Adefovir at a dose of 10 mg daily, although active against HBV, has minimal anti-HIV activity, and HIV resistance has not been observed to develop in patients receiving adefovir at this dose for 48 weeks. Adefovir is now Food and Drug Administration (FDA) approved for adults who require treatment for chronic hepatitis B but do not yet require treatment for their HIV infection (**CIII**). Adefovir can cause renal tubular disease when administered in high dosage, but

this is less common at the 10 mg/day dose for treatment of chronic hepatitis B. Safety and effectiveness of adefovir in pediatric patients has not yet been established.

Tenofovir, a nucleotide analogue similar to adefovir, has in vitro activity against HBV, but data is limited in subjects with HIV-HBV coinfection. It has been administered in certain adult patients at a dose used for treatment of HIV (tenofovir administered as 300 mg once daily). Similar to 3TC, tenofovir, when used for treatment of chronic hepatitis B among HIV-infected patients, should be administered as part of a fully suppressive HAART regimen and not as monotherapy (**CIII**). No data are available on safety and appropriate dosing of tenofovir among children.

Definitions

Quality of Evidence Supporting the Recommendations

I: Evidence from at least one 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.

Strength of the Recommendation

Rating: A

Strength of recommendation: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use.

Should always be offered.

Rating: B

Strength of recommendation: Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use.

Should generally be offered.

Rating: C

Strength of recommendation: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g. drug toxicity, drug interactions) or cost of the treatment or alternative approaches.

Optional.

Rating: D

Strength of recommendation: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Should generally not be offered.

Rating: E

Strength of recommendation: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Should never be offered.

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)-exposed and -infected children

POTENTIAL HARMS

Complications of Diagnostic Tests

- Complications of induced sputum analysis can include nausea, vomiting, and bronchospasm
- Complications of bronchoscopy with bronchoalveolar lavage included hemoptysis, pneumothorax, transient increase in hypoxemia, transient increase in pulmonary infiltrates at the lavage site, and postbronchoscopy fever
- Complications of fiberoptic bronchoscopy include pneumothorax and hemorrhage
- Complications of open-lung biopsy include pneumothorax, pneumomediastinum, and hemorrhage

Adverse Effects and Drug Interactions

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, appendices at the end of the original guideline document provide information on pediatric drug preparations and major toxicities (Appendix B), and provide information about clinically significant drug interactions for the drugs recommended for treatment of individual opportunistic infections among children (Appendix C).

CONTRAINDICATIONS

CONTRAINDICATIONS

- Fiberoptic bronchoscopy with transbronchial biopsy is contraindicated among children with thrombocytopenia.
- Primaquine is contraindicated among patients with glucose-6-dehydrogenase deficiency associated with the possibility of inducing hemolytic anemia.
- Rifampin induces hepatic cytochrome P450 enzymes and can accelerate clearance of drugs metabolized by the liver (e.g., protease inhibitors and non-nucleoside reverse transcriptase inhibitors), resulting in subtherapeutic levels of the drug. As a result, concurrent administration of rifampin and single protease inhibitors, with the exception of ritonavir, is not recommended. Coadministration of ritonavir-boosted saquinavir, with 400 mg ritonavir boosting, with rifampin is possible, but low-dose ritonavir-boosted dual protease inhibitor regimens should not be used. Concurrent administration of rifampin with the non-nucleoside reverse transcriptase inhibitor delavirdine also is contraindicated because of similar drug interactions.
- Treatment with interferon-alfa-based therapies is contraindicated in children with decompensated liver disease, significant cytopenias, severe renal or cardiac disorders, and autoimmune disease.
- Interferon-alfa monotherapy can be used among children with contraindications to ribavirin who cannot receive combination therapy (e.g., unstable cardiopulmonary disease, severe preexisting anemia, or hemoglobinopathy).
- Ribavirin is contraindicated in children with unstable cardiopulmonary disease, preexisting anemia or hemoglobinopathy.

A list of drug contraindications is provided in Appendix C of the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Treatment of opportunistic infections is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated.

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
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references] PubMed

ADAPTATION

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

DATE RELEASED

2004 Dec 3

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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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.

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:

- A comprehensive Spanish-language Web site featuring information about HIV treatment and clinical trials is available at http://aidsinfo.nih.gov/infoSIDA/.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 20, 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 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 July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs.

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Date Modified: 11/3/2008


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