Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children

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

These guidelines are updated regularly to provide current information. The most recent information is available at **http://AIDSinfo.nih.gov**.

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Background

Opportunistic Infections in HIV-Infected Children in the Era of Potent Antiretroviral Therapy

In the pre-antiretroviral era and prior to the development of potent combination highly active antiretroviral treatment (HAART) regimens, opportunistic infections (OIs) were the primary cause of death in human immunodeficiency virus (HIV)-infected children *[1]*. Current HAART regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial and dramatic decrease in acquired immunodeficiency syndrome (AIDS)-related OIs and deaths in adults and also in children *[2-4]*. In an observational study from pediatric clinical trial sites in the United States, PACTG 219, the incidence of the most common initial OIs in children in the potent HAART era (2000 – 2004) was substantially lower than the incidence in children followed at the same sites during the pre-HAART era (1988 – 1998) *[1, 3]*. For example, the incidence per 100 child-years for bacterial pneumonia decreased from 11.1 in the pre-HAART era to 2.2 in the HAART era; bacteremia from 3.3 to 0.4; herpes zoster from 2.9 to 1.1; disseminated *Mycobacterium avium* complex (MAC) from 1.8 to 0.14; and *Pneumocystis jirovecii* pneumonia (PCP) from 1.3 to 0.09.

Despite this progress, prevention and management of OIs remain critical components of care for HIV-infected children. OIs continue to be the presenting symptom of HIV infection among children whose HIV-exposure status is not known (e.g., due to lack of maternal antenatal HIV testing). For children with known HIV infection, there may be barriers, such as parental substance abuse, that may limit linkage to appropriate care where evaluation of indications for prophylaxis would occur. For HIV-infected children in care, suboptimal quality of care may result in children who are eligible for primary or secondary OI prophylaxis failing to receive it. Additionally, adherence to multiple drugs (antiretroviral drugs and concomitant OI prophylaxis drugs) may prove difficult for the child or family. Multiple drug-drug interactions of OI, antiretroviral, and other drugs resulting in increased adverse events and treatment efficacy may limit the choice and continuation of both HAART and prophylaxis regimens. OIs continue to occur in children who have virologic and immunologic failure due to drug resistance. In PACTG 219, lack of a sustained response to HAART was predictive of the occurrence of OIs in children *[5]*. Finally, immune reconstitution inflammatory syndrome (IRIS), initially described in HIV-infected adults but also seen in HIV-infected children, can complicate treatment of OIs when starting HAART or when trying to optimize a failing regimen in a patient with acute OI. Thus, the prevention and treatment of OIs in HIV-infected children remains important even in an era of potent HAART.

History of the Guidelines

In 1995, the U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) developed guidelines for preventing OIs among adults, adolescents, and children infected with HIV *[6]*. These guidelines, developed for health care providers and their HIV-infected patients, were revised in 1997, 1999, and 2002 *[7, 8]*. In 2001, the National Institutes of Health (NIH), IDSA, and the Centers for Disease Control and Prevention (CDC) convened a working group to develop guidelines for treatment of HIV-associated OIs, with a goal of providing evidence-based guidelines on treatment and prophylaxis. In recognition of unique considerations for HIV-infected infants, children, and adolescents, including differences between adults and children in mode of acquisition, natural history, diagnosis, and treatment of HIV-related OIs, a separate Pediatric OI Guidelines working group was established. The pediatric OI treatment guidelines were initially published in 2005 *[9]*.

The current document combines recommendations for prevention and treatment of OIs in HIV-exposed and -infected children into one document; it accompanies a similar document on prevention and treatment of OIs

among HIV-infected adults prepared by a separate group of adult HIV and infectious disease specialists. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research (OAR) of the NIH. Pediatric specialists with expertise in specific OIs were selected to review the literature since the last publication of the prevention and treatment guidelines, conferred over a period of several months, and produced draft guidelines. Recommendations were reviewed and discussed by the Pediatric OI Working Group at a meeting in Bethesda, Maryland, on June 25 – 26, 2007. The final document was prepared after this meeting, reflecting the discussion and further revisions at that meeting.

Why Pediatric Prevention and Treatment Guidelines?

An important mode of acquisition of OIs as well as HIV infection among children is from their infected mother. HIV-infected women coinfected with opportunistic pathogens might be more likely to transmit these infections to their infants than women without HIV infection. For example, greater rates of perinatal transmission of hepatitis C and cytomegalovirus (CMV) have been reported from HIV-infected versus -uninfected women *[10, 11]*. In addition, HIV-infected women or HIV-infected family members coinfected with certain opportunistic pathogens might be more likely to transmit these infections horizontally to their children, resulting in an increased likelihood of primary acquisition of such infections in the young child. For example, *Mycobacterium tuberculosis* infection among children primarily reflects acquisition from family members with active tuberculosis (TB) disease, and increased incidence and prevalence of TB among HIV-infected persons is well documented. HIV-exposed or -infected children in the United States might have a higher risk for exposure to *M. tuberculosis* than comparably aged children in the general U.S. population because of residence in households with HIV-infected adults *[12]*. Therefore, infections with opportunistic pathogens might affect not just HIV-infected infants but also HIV-exposed but uninfected infants who become infected by the pathogen because of transmission from HIV-infected mothers or family members with coinfections. Guidelines for treatment of OIs in children must include consideration of the treatment of infections occurring among all children – both HIV infected and uninfected – born to HIV-infected women.

The natural history of OIs among children might differ from that observed among HIV-infected adults. Many OIs in adults are secondary to reactivation of opportunistic pathogens, which were often acquired before HIV infection at a time when host immunity was intact. However, OIs among HIV-infected children more often reflect primary infection with the pathogen. In addition, among children with perinatal HIV infection, the primary infection with the opportunistic pathogen occurs after HIV infection is established and the child's immune system might already be compromised. This can lead to different manifestations of disease associated with the pathogen among children than among adults. For example, young children with TB are more likely to have nonpulmonic and disseminated infection than adults, even without concurrent HIV infection.

Multiple difficulties exist in making laboratory diagnosis of various infections in children. Diagnosis is often compounded by a child's inability to describe the symptoms of disease. For infections where the primary diagnostic modality is the presence of specific antibodies (e.g., the hepatitis viruses and CMV), the ability to make a diagnosis in young infants is complicated by transplacental transfer of maternal antibodies that can persist in the infant for up to 18 months. Assays capable of directly detecting the pathogen are required to definitively diagnose such infections in infants. In addition, diagnosing the etiology of lung infections among children can be difficult because they do not generally produce sputum, and more invasive procedures might be needed.

Data related to the efficacy of various therapies for OIs in adults can generally be extrapolated to children, but issues related to drug pharmacokinetics, formulation, ease of administration, and drug dosing and toxicity require special considerations among children. Young children in particular metabolize drugs

differently from adults and older children and the volume of distribution differs. Unfortunately, data on appropriate drug dosing recommendations for children aged <2 years often are lacking.

The frequency of different opportunistic pathogens among HIV-infected children in the pre-HAART era varied by age, pathogen, previous OI, and immunologic status *[1]*. In the pre-HAART era, the most common OIs among children in the United States (event rates >1.0 per 100 child-years) were serious bacterial infections (with pneumonia, often presumptively diagnosed, and bacteremia being most common), herpes zoster, disseminated MAC, PCP, and candidiasis (esophageal and tracheobronchial disease). Less commonly observed OIs (event rate <1.0 per 100 child-years) included CMV disease, cryptosporidiosis, TB, systemic fungal infections, and toxoplasmosis *[3, 4]*. History of a previous AIDS-defining OI was a predictor of developing a new infection. Although the majority of infections occurred among children who were substantially immunocompromised, serious bacterial infections, herpes zoster, and TB occurred across the spectrum of immune status.

Descriptions of OIs in the HAART era among children have been limited. As with HIV-infected adults, substantial decreases in mortality and morbidity, including OIs, have been observed among children receiving HAART *[2]*. Although the number of OIs has substantially decreased in the HAART era, HIV-associated OIs and other related infections continue to occur among HIV-infected children *[3, 13]*.

In comparison with recurrent serious bacterial infections, some of the protozoan, fungal, or viral OIs complicating HIV are not curable with available treatments. Sustained, effective HAART, resulting in improved immune status, has been established as the most important factor in control of OIs among both HIV-infected adults and children *[14]*. For many OIs, following treatment of the initial infectious episode, secondary prophylaxis in the form of suppressive therapy is indicated to prevent recurrent clinical disease from reactivation or reinfection *[15]*.

These guidelines serve as a companion to the ***USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults*** *[16]*. Treatment of OIs 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.

Because the guidelines target HIV-exposed and -infected children in the United States, the opportunistic pathogens discussed are those common to the United States and do not include certain pathogens (e.g., *Penicillium marneffei*) that might be seen more frequently in resource-limited countries. The document is organized to provide information about the epidemiology, clinical presentation, diagnosis, and treatment for each pathogen. Each treatment recommendation is accompanied by a rating that includes a letter and a Roman numeral and is similar to the rating systems used in other USPHS/IDSA guidelines *[17]*. The letter indicates the strength of the recommendation, which is based on the opinion of the Working Group, and the Roman numeral reflects the nature of the evidence supporting the recommendation (Box).

Tables at the end of this document summarize recommendations for prevention of OIs in children (Tables 1 – 3); treatment of OIs in children (Table 4); drug preparation and toxicity information for children (Table 5); drug-drug interactions (Table 6), and immunization recommendations for HIV-infected children and adolescents (Figures 1 and 2).

Box: Rating Scheme for Prevention and Treatment Recommendations	
Category	**Definition**
A	Both strong evidence for efficacy and substantial clinical benefit support recommendations for use. **Should always be offered.**
B	Moderate evidence for efficacy – or strong evidence for efficacy but only limited clinical benefit – support recommendations for use. **Should generally be offered.**
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. **Optional.**
D	Moderate evidence for lack of efficacy or for adverse outcomes supports a recommendation against use. **Should generally not be offered.**
E	Good evidence for lack of efficacy or for adverse outcomes supports a recommendation against use. **Should never be offered.**
Quality of evidence supporting the recommendation	
I	Evidence from at least one properly designed randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled 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.

Diagnosis of HIV Infection and Presumptive Lack of HIV Infection in Children with Perinatal HIV Exposure

Because of persistence of maternal antibody for up to 18 months of age, virologic tests (generally HIV DNA or RNA assays) are needed to determine infection status in children aged <18 months. The CDC surveillance definition states a child is viewed as definitively infected if they have positive virologic results on two separate specimens or if they are aged >18 months and have either a positive virologic test or a positive confirmed HIV antibody test.

CDC has revised laboratory criteria to allow presumptive exclusion of HIV infection at an earlier age for surveillance purposes. A child who has not been breastfed is presumptively uninfected if they have no clinical or laboratory evidence of HIV infection and have two negative virologic tests, both of which were obtained at ≥2 weeks of age and one of which was obtained at ≥4 weeks of age, and no positive tests; or a single negative virologic test at ≥8 weeks of age and no positive tests; or one negative HIV antibody test at ≥6 months of age. Definitive lack of infection is confirmed by having two negative viral tests, both of which were obtained at ≥1 month of age and one of which was obtained at ≥4 months of age, or at least two negative HIV antibody tests from separate specimens obtained at ≥6 months of age. The new presumptive definition of uninfected may allow clinicians to avoid starting PCP prophylaxis in some HIV-exposed infants at age 6 weeks (see PCP section).

Antiretroviral Therapy and Management of Opportunistic Infections

Studies in adults and children have demonstrated that HAART reduces the incidence of OIs and improves survival, independent of the use of OI antimicrobial prophylaxis. HAART can lead to the improvement or resolution of certain OIs, particularly ones such as cryptosporidiosis or microsporidiosis infection, where an effective specific treatment is not available. However, potent HAART does not replace the need for OI prophylaxis in children with severe immune suppression. Additionally, initiation of HAART in the setting of an acute or latent OI can lead to IRIS, an exaggerated inflammatory reaction that can cause clinical worsening of disease and require use of anti-inflammatory drugs (see IRIS section below).

Specific data to guide recommendations for when to start HAART in the setting of an acute OI in children and the management of HAART when an acute OI occurs in a child already receiving HAART are limited. The decision of when to start HAART in a child with an acute or latent OI needs to be individualized and will vary depending on the degree of immunologic suppression in the child prior to starting HAART. Similarly, in a child already receiving HAART who develops an OI, management will need to take into account the child's clinical, viral, and immune status on HAART and the potential drug-drug interactions between the HAART and the required OI drug regimen.

Immune Reconstitution Inflammatory Syndrome (IRIS)

As in adults, antiretroviral therapy improves immune function and CD4 cell count in HIV-infected children; within the first few months of starting treatment, HIV viral load sharply decreases and the CD4 count rapidly increases. This leads to an increased capacity to mount inflammatory reactions. After initiation of HAART, some patients develop a paradoxical inflammatory response by their reconstituted immune system to infectious or noninfectious antigens, resulting in apparent clinical worsening. This is referred to as IRIS, and while primarily reported in adults initiating therapy, it has also been reported in children *[18-28]*.

IRIS can occur following the initiation of HAART due to worsening of an existing active, latent, or occult OI, where infectious pathogens that were previously not recognized by the immune system now evoke an immune response. This inflammatory response is often exaggerated compared to the response occurring in patients with a normal immune system (referred to by some experts as Immune Reconstitution Disease). An example is activation of latent or occult TB following initiation of ART (referred to by some experts as "unmasking IRIS"). Alternatively, there can be clinical recrudescence of a successfully treated infection, with a paradoxical, symptomatic relapse despite microbiologic treatment success and sterile cultures (referred to by some experts as "paradoxical IRIS"). In this case, there is reconstitution of antigen-specific T-cell-mediated immunity with activation of the immune system following initiation of HAART against persisting antigens, whether present as dead, intact organisms or debris.

The pathologic process of IRIS is inflammatory and not microbiologic in etiology. Thus, distinguishing IRIS from treatment failure, antimicrobial resistance, or noncompliance is important. In cases of therapeutic failure, a microbiologic culture should reveal the continued presence of an infectious organism, whereas in cases of IRIS, follow-up cultures should be sterile.

Description of IRIS primarily comes from adult case reports. A proposed clinical definition is worsening symptoms of inflammation or infection temporally related to starting HAART that are not explained by newly acquired infection or disease, the usual course of a previously acquired disease, or HAART toxicity in a patient with $\geq$1 $\log_{10}$ decrease in plasma HIV RNA *[29]*.

The timing of occurrence of IRIS following initiation of HAART in adults has been variable, with the majority of cases occurring during the first 2 to 3 months post-initiation; however, as many as 30% can present beyond the first 3 months of treatment. Later onset IRIS may be due to an immune reaction against persistent noninfectious antigen. Antigen clearance is variable but persists long after microbiologic sterility. For example, following pneumococcal bacteremia, the C-polysaccharide antigen can be identified in the urine of 40% of HIV-infected adults 1 month after successful treatment; similarly, mycobacterial DNA can persist several months past culture viability.

In adults, IRIS has most frequently been observed following initiation of therapy in individuals with mycobacterial infections (including MAC and *Mycobacterium tuberculosis*), PCP, cryptococcal infection, CMV, varicella zoster or herpes virus infections, hepatitis B and C infections, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). In children, reactions have also been described in

children who had received Bacille Calmette-Guérin (BCG) vaccine and later initiated HAART *[22, 25, 26, 28]*. In a study of 153 symptomatic children with CD4 <15% at initiation of therapy in Thailand, the incidence of IRIS was 19%, with a median time of onset of 4 weeks following start of HAART; children who developed IRIS had lower baseline CD4 percentage compared to those who did not *[24]*.

No randomized controlled trials have been published evaluating treatment of IRIS, and treatment has been based on severity of disease **(CIII)**. For mild cases, observation alone with close clinical and laboratory monitoring may be sufficient. For moderate cases, nonsteroidal anti-inflammatory drugs have been used to ameliorate symptoms. For severe cases, corticosteroids, such as dexamethasone, have been used. However, the optimal dosing and duration of therapy are currently unknown, and inflammation can take weeks to months to subside. During this time HAART should be continued.

Initiation of HAART in the Setting of an Acute OI in Treatment-Naïve Children

The ideal time to initiate HAART in the setting of an acute OI is unknown. The benefit of initiation of HAART is improved immune function, which could result in faster resolution of the OI. This is particularly important for OIs for which there are limited or no effective therapeutic options available, such as cryptosporidiosis, microsporidiosis, PML, and Kaposi's sarcoma (KS). However, there are potential problems with initiation of HAART at the same time treatment for the OI is started. These include drug-drug interactions between the antiretroviral and antimicrobial drugs, particularly given the limited repertoire of antiretroviral drugs available for children compared to adults; issues related to toxicity, including potential additive toxicity of antiretroviral and OI drugs as well as difficulty in distinguishing HAART toxicity from OI treatment toxicity; and the potential for IRIS syndromes to complicate OI management.

The primary consideration in delaying HAART until after initial treatment of the acute OI has been received is the risk of death during the period of delay. While the short-term risk of death in the United States during a 2-month HAART delay may be relatively low, the mortality in resource-limited countries is significant. IRIS events are more likely to occur in persons with advanced HIV infection and higher OI-specific antigenic burdens, such as those with disseminated infections or who have a shorter time from an acute OI onset to starting HAART. However, in the absence of an OI with central nervous system (CNS) involvement, such as cryptococcal meningitis, the majority of IRIS events, while potentially resulting in significant morbidity, do not result in mortality. With CNS IRIS or in resource-limited countries, significant IRIS-related mortality may occur with simultaneous initiation of HAART and OI treatment; however, significant mortality in the absence of HAART also occurs.

Since there are no randomized trials in either adults or children to address the optimal time for initiation of HAART in the setting of an acute OI, decisions need to be individualized for each child. The timing is a complex decision based on the severity of HIV disease, efficacy of standard OI-specific treatment, social support system, medical resource availability, potential drug-drug interactions, and risk of IRIS. Most experts feel that for children who have OIs that lack effective treatment (e.g., cryptosporidiosis, microsporidiosis, PML, KS), the early benefit of potent HAART outweighs any increased risk, and potent HAART should be initiated as soon as possible **(AIII)**. For other OIs, such as TB, MAC, PCP, and cryptococcal meningitis, awaiting a response to therapy may be warranted before initiating HAART **(CIII)**.

Management of Acute OIs in HIV-Infected Children Receiving HAART

OIs occurring in HIV-infected children soon after initiation of HAART (within 12 weeks) may be subclinical infections that are unmasked by HAART-related improvement in immune function, also known as "unmasking IRIS". This usually occurs in children who have more severe immune suppression at the time HAART is initiated. This does not represent a failure of HAART therapy, but rather a sign of

immune reconstitution (see IRIS section). In such situations, HAART should be continued and treatment for the OI initiated **(AIII)**. It is important to assess whether there are any drug-drug interactions of concern between the antiretroviral and antimicrobial drugs and whether any treatment modifications need to be made.

In children who develop an OI after receiving >12 weeks of HAART with virologic and immunologic response to therapy, it can be difficult to distinguish between later onset IRIS (such as a "paradoxical IRIS" reaction where the reconstituted immune system demonstrates an inflammatory reaction to a noninfectious antigen) and incomplete immune reconstitution with HAART allowing occurrence of a new OI. In such situations, HAART should be continued and if microbiologic evaluation demonstrates organisms by stain or culture, specific OI-related therapy should be initiated **(AII)**. If the CD4 cell response to HAART appears suboptimal, reassessment of the HAART regimen may be considered as per the pediatric antiretroviral guidelines (see ***Recommendations for the Use of Antiretroviral Agents in Pediatric HIV Infection***) *[14]* **(BIII)**.

OIs can also occur in HIV-infected children who are experiencing virologic and immunologic failure on HAART and represent clinical failure of therapy. In this situation, treatment of the OI should be initiated, viral resistance testing performed, and the child's HAART regimen should be reassessed, as described in the pediatric antiretroviral guidelines (see ***Recommendations for the Use of Antiretroviral Agents in Pediatric HIV Infection***) *[14]* **(AI)**.

Prevention of Vaccine-Preventable Diseases in Children and Adolescents with HIV Infection

Vaccines are extremely effective primary prevention tools and vaccines that protect against 16 diseases are recommended for routine use in children and adolescents in the United States. Immunization schedules for children aged 0 to 6 years and 7 to 18 years are published annually (**http://www.cdc.gov/vaccines/recs/schedules/default.htm**). These schedules are compiled from approved vaccine-specific policy recommendations and are harmonized between the major vaccine policy setting and vaccine delivery organizations (e.g., Advisory Committee on Immunization Practices [ACIP], American Academy of Pediatrics, American Association of Family Physicians).

HIV-infected children should be protected from vaccine-preventable diseases. Most vaccines recommended for routine use can be safely administered to HIV-exposed or -infected children. The recommended immunization schedules for HIV-exposed and -infected children aged 0 to 6 years and 7 to 18 years were approved by the ACIP through October 2007 (Figures 1 and 2). Guidance on use of rotavirus vaccine in HIV-exposed and -infected children was approved by the ACIP in June 2007. These schedules will be updated annually to reflect additional vaccine recommendations that are approved by the ACIP and pertain to HIV-exposed or -infected children.

All inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. If inactivated vaccines are indicated for persons with altered immunocompetence, the usual doses and schedules are recommended. However, the effectiveness of such vaccinations might be suboptimal *[30]*.

Persons with severe cell-mediated immune deficiency should not receive live attenuated vaccines. However, children with HIV infection are at increased risk for complications of varicella, herpes zoster, and measles compared with immunocompetent children. On the basis of limited safety, immunogenicity, and efficacy data among HIV-infected children, varicella and MMR vaccines can be considered for HIV-infected children who are not severely immunosuppressed (i.e., those with age-specific CD4 cell percentages of ≥15%) *[30-32]*. No safety or efficacy data are available for the administration of rotavirus

vaccine to infants who are potentially immunocompromised, including those who are HIV infected *[33]*. However, the following considerations support vaccination of HIV-exposed or -infected infants: (1) HIV diagnosis may not be established in infants born to HIV-infected mothers before the age of the first rotavirus vaccine dose, (2) only 1.5% – 3% of HIV-exposed infants in the United States will eventually be diagnosed with HIV infection, and (3) Rotateq vaccine (the only rotavirus vaccine currently licensed in the United States for prevention of rotavirus gastroenteritis) is considerably attenuated.

Consult the specific ACIP statements (available at **http://www.cdc.gov/vaccines/pubs/ACIP-list.htm**) for recommendations, precautions, and contraindications for use of specific vaccines *[31-44]*.

BACTERIAL INFECTIONS:
Serious and Recurrent

Epidemiology

In the pre-HAART era, serious bacterial infections were the most commonly diagnosed OI in HIV-infected children, with an event rate of 15 per 100 child-years *[1]*. Pneumonia was the most common bacterial infection (11 per 100 child-years), followed by bacteremia (3 per 100 child-years) and urinary tract infection (2 per 100 child-years). Other serious bacterial infections, including osteomyelitis, meningitis, abscess, and septic arthritis, occurred at rates <0.2 per 100 child-years. More minor bacterial infections such as otitis media and sinusitis were particularly common, occurring at a rate of 17 – 85 per 100 child-years in untreated HIV-infected children *[45]*.

With the advent of HAART, the rate of pneumonia has decreased to 2.2 – 3.1 per 100 child-years *[3, 46]*, similar to the rate of 3 – 4 per 100 child-years seen in uninfected children *[47, 48]*. The rate of bacteremia/sepsis in the HAART era has also decreased dramatically to 0.35 – 0.37 per 100 child-years *[3, 4, 46]*, but this rate remains substantially higher than the rate of <0.01 per 100 child-years in HIV-uninfected children *[49, 50]*. Sinusitis and otitis rates among HAART-treated children are substantially reduced (2.9 – 3.5 per 100 child-years) but remain higher than rates in children who do not have HIV infection *[46]*.

Acute pneumonia, often presumptively diagnosed in children, was associated with increased risk for long-term mortality among HIV-infected children in one study in the pre-HAART era *[51]*. HIV-infected children with pneumonia are more likely to be bacteremic and to die than uninfected children with pneumonia *[52]*. Chronic lung disease might predispose persons to development of acute pneumonia; in one study, the incidence of acute lower respiratory tract infection in HIV-infected children with chronic lymphoid interstitial pneumonitis was approximately 10-fold higher than in a community-based study of HIV-uninfected children *[53]*. Chronically abnormal airways are likely more susceptible to infectious exacerbations (similar to those seen in children and adults with bronchiectasis or cystic fibrosis) caused by typical respiratory bacteria (*S. pneumoniae*, non-typeable *H. influenzae*) as well as *Pseudomonas* spp.

Streptococcus pneumoniae is the most prominent invasive bacterial pathogen in children with HIV infection both in the United States and worldwide, accounting for >50% of bacterial bloodstream infections in HIV-infected children *[1, 4, 54-57]*. HIV-infected children have a markedly increased risk for pneumococcal infection compared with those who are not HIV infected *[58, 59]*. In the absence of HAART, the incidence of invasive pneumococcal disease was 6.1 per 100 child-years among HIV-infected children through age 7 years *[60]*, whereas among children treated with HAART, the rate of invasive pneumococcal disease is decreased by about half, to 3.3 per 100 child-years *[46]*. This is consistent with the halving of invasive pneumococcal disease rates in HIV-infected adults receiving HAART compared to rates in those not receiving HAART *[61]*. Among children with invasive pneumococcal infections, studies vary on whether penicillin-resistant pneumococcal strains are more commonly isolated from HIV-infected than uninfected persons *[56, 60, 62-64]*. Reports among children without HIV infection have not demonstrated a difference in the case-fatality rate between those with penicillin-susceptible versus -nonsusceptible pneumococcal infections (case-fatality rate was associated with severity of disease and underlying illness) *[65]*. In one pediatric study, invasive disease due to penicillin-nonsusceptible pneumococcus was associated with longer fever and hospitalization but not with greater risk of complications or poorer outcome *[66]*. After routine use of 7-valent pneumococcal conjugate vaccine since 2000, the overall incidence of drug-resistant pneumococcal infections has stabilized or decreased.

Haemophilus influenzae type b (Hib) also has been reported to be more common in HIV-infected children before availability of Hib vaccine. In a study in South African children who had not received Hib conjugate vaccine, the estimated relative annual rate of overall invasive Hib disease in children aged <1 year was 5.9 times greater among HIV-infected than uninfected children, and HIV-infected children were also at greater risk for having bacteremic pneumonia *[67]*. However, Hib is unlikely to occur in HIV-infected children in most U.S. communities, where high rates of Hib immunization lead to very low rates of Hib nasopharyngeal colonization among contacts.

HIV-related immune dysfunction may increase the risk of invasive meningococcal disease in HIV-infected patients, but few cases have been reported *[68-72]*. In a population-based study of invasive meningococcal disease in Atlanta, Georgia *[72]*, there was, as expected, a higher annual rate of disease among 18 – 24 year olds (1.17 per 100,000) compared to that of all adults (0.5 per 100,000), but the estimated annual rate among HIV-infected adults was substantially higher (11.2 per 100,000). There may be an increased risk of invasive meningococcal disease in HIV-infected adults. Specific data for risk of meningococcal disease in younger HIV-infected children are not available.

Although the frequency of gram-negative bacteremia is lower than gram-positive bacteremia among HIV-infected children, gram-negative bacteremia is more common among children with advanced HIV disease or immunosuppression and those with central venous catheters. However, in children aged <5 years, gram-negative bacteremia also was observed among children with milder levels of immune suppression. In a study of 680 HIV-infected children in Miami, Florida, through 1997, a total of 72 (10.6%) had 95 episodes of gram-negative bacteremia; the predominant organisms identified in those with gram-negative bacteremia were *Pseudomonas aeruginosa* (26%), nontyphoidal *Salmonella* (15%), *Escherichia coli* (15%), and *Haemophilus influenzae* (13%) *[73]*. The relative frequency of the organisms varied over time, with the relative frequency of *P. aeruginosa* bacteremia increasing from 13% before 1984 to 56% during 1995 – 1997 and *Salmonella* from 7% before 1984 to 22% during 1995 – 1997. However, *H. influenzae* was not observed after 1990 (presumably decreasing after incorporation of Hib vaccine into routine childhood vaccinations). The overall case-fatality rate for gram-negative bacteremia was 43%. Among Kenyan children with bacteremia, HIV infection increased the risk of nontyphoidal *Salmonella* and *E. coli* infections *[74]*.

The presence of a central venous catheter increases the risk for bacterial infections in HIV-infected children, and the incidence is similar to that observed among children with cancer. The most commonly isolated pathogens in catheter-associated bacteremia in HIV-infected children are similar to those in HIV-negative children with indwelling catheters, including coagulase-negative staphylococci, *S. aureus*, enterococci, *P. aeruginosa*, gram-negative enteric bacilli, *Bacillus cereus*, and *Candida* spp. *[57, 75]*.

Data are conflicting as to whether infectious morbidity is increased in HIV-exposed but uninfected children. In studies in developing countries, uninfected infants of HIV-infected mothers have higher mortality (primarily due to bacterial pneumonia and sepsis) than those born to uninfected mothers *[76, 77]*. Advanced maternal HIV infection was associated with increased risk of death *[76, 77]*. In a study in Latin America and the Caribbean, 60% of 462 uninfected infants of HIV-infected mothers experienced infectious disease morbidity during the first 6 months of life, with the rate of neonatal infections (particularly sepsis) and respiratory infections higher than rates in comparable community-based studies *[78]*. Among other factors, infections were associated with more advanced maternal HIV disease and maternal smoking during pregnancy. However, in a study from the United States, the rate of lower respiratory tract infections in HIV-exposed, uninfected children was within the range reported for normal children in the first year of life *[79]*. In a separate study, the rate of overall morbidity (including but not specific to infections) decreased between 1990 and 1999 in HIV-exposed, uninfected children *[80]*, although no comparison of rates was made to an HIV-unexposed or community-based cohort.

Clinical Manifestations

Clinical presentation will be dependent on the particular type of bacterial infection (e.g., bacteremia/sepsis, osteomyelitis/septic arthritis, pneumonia, meningitis, and sinusitis/otitis media) *[81]*. HIV-infected children with invasive bacterial infections typically have a clinical presentation similar to children without HIV infection, with an acute presentation and fever *[59, 60, 82]*. HIV-infected children might be less likely than children without HIV infection to have leukocytosis *[60]*.

The classical signs, symptoms, and laboratory test abnormalities that usually indicate invasive bacterial infection (e.g., fever and elevated white blood cell [WBC] count) are usually present but might be lacking among HIV-infected children having reduced immune competence *[59, 81]*. One-third of HIV-infected children not receiving HAART who experience acute pneumonia have recurrent episodes *[51]*. Resulting lung damage before HAART was initiated can then lead to continued recurrent pulmonary infections, even in the presence of effective HAART.

In studies in Malawian and South African children with acute bacterial meningitis, the clinical presentation of children with and without HIV infection was similar *[83, 84]*. However, in the Malawi study, HIV-infected children were 6.4-fold more likely to have repeated episodes of meningitis than children without HIV infection, although the study did not differentiate recrudescence from new infections *[83]*. In both studies, HIV-infected children were more likely to die of meningitis than children without HIV infection.

Diagnosis

Attempted isolation of a pathogenic organism from normally sterile sites (e.g., blood, cerebrospinal fluid [CSF], and pleural fluid) is strongly recommended. This is particularly important because of an increasing incidence of antimicrobial resistance, including penicillin-resistant *S. pneumoniae* and community-acquired methicillin-resistant *S. aureus* (MRSA).

Because of difficulties obtaining appropriate specimens (e.g., sputum) from young children, bacterial pneumonia is most often a presumptive diagnosis in a child with fever, pulmonary symptoms, and an abnormal chest radiograph unless an accompanying bacteremia exists. In the absence of a laboratory isolate, differentiating viral from bacterial pneumonia using clinical criteria can be difficult *[85]*. In a study of IVIG prophylaxis of bacterial infections, only 12% of acute presumed bacterial pneumonia episodes had a bacterial pathogen identified *[51]*. TB and PCP must always be considered in HIV-infected children with pneumonia. Presence of wheezing makes an acute bacterial pneumonia less likely than other causes, such as viral pathogens, asthma exacerbation, “atypical” bacterial pathogens such as *Mycoplasma pneumoniae*, or aspiration. Sputum induction obtained by nebulization with hypertonic (5%) saline has been evaluated for diagnosis of pneumonia in 210 South African infants and children (median age: 6 months), 66% of whom had HIV infection *[86]*. The procedure was well tolerated and identified an etiology in 63% of children with pneumonia (identification of bacteria in 101, *M. tuberculosis* in 19, and PCP in 12 children). Culture of blood and pleural fluid, if present, should be done.

Among children with bacteremia, a source for the bacteremia should be sought. In addition to routine chest radiographs, other diagnostic radiologic evaluations (e.g., abdomen and ultrasound studies) might be necessary among HIV-infected children with compromised immune systems to identify less apparent foci of infection (e.g., bronchiectasis, internal organ abscesses) *[87-89]*. Among children with central venous catheters, both a peripheral and catheter blood culture should be obtained; if the catheter is removed, the catheter tip should be sent for culture. Assays for detection of bacterial antigens or evidence by molecular biology techniques are important for the diagnostic evaluation of HIV-infected children in whom unusual

pathogens might be involved or difficult to identify or culture by standard techniques. For example, *Bordetella pertussis* and *Chlamydia pneumoniae* can be identified by a polymerase chain reaction (PCR) assay of nasopharyngeal secretions *[85]*.

Prevention Recommendations

Preventing Exposure

Because *Streptococcus pneumoniae* and *Haemophilus influenzae* are common in the community, no effective way exists to eliminate exposure to these bacteria. However, routine use of conjugated 7-valent pneumococcal conjugate and Hib vaccines in U.S. infants has dramatically reduced vaccine type invasive disease and nasopharyngeal colonization, conferring herd protection of HIV-infected contacts due to decreased exposure to Hib and pneumoccal serotypes included in the vaccine.

Food. In order to reduce the risk of exposure to potential gastrointestinal (GI) bacterial pathogens, health care providers should advise that HIV-infected children avoid eating the following raw or undercooked foods (including other foods that contain them): eggs, poultry, meat, seafood (especially raw shellfish), and raw seed sprouts. Unpasteurized dairy products and unpasteurized fruit juices should also be avoided **(BIII)**. Of particular concern to HIV-infected infants and children is the potential for caretakers to handle these raw foods (e.g., during meal preparation) and then unknowingly transfer bacteria from their hands to the child's food, milk, formula, or directly to the child. Hands, cutting boards, counters, knives, and other utensils should be washed thoroughly after contact with uncooked foods **(BIII)**. Produce should be washed thoroughly before being eaten **(BIII)**.

Pets. When obtaining a new pet, caregivers should avoid dogs or cats aged <6 months or stray animals **(BIII)**. HIV-infected children and adults should avoid contact with any animals that have diarrhea and should wash their hands after handling pets, including before eating, and avoid contact with pets' feces **(BIII)**. HIV-infected children should avoid contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) as well as chicks and ducklings because of the risk for salmonellosis **(BIII)**.

Travel. The risk for foodborne and waterborne infections among immunosuppressed, HIV-infected persons is magnified during travel to economically developing countries. HIV-infected children who travel to such countries should avoid foods and beverages that might be contaminated, including raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items sold by street vendors **(AII)**. Foods and beverages that are usually safe include steaming hot foods, fruits that are peeled by the traveler, bottled (including carbonated) beverages, and water brought to a rolling boil for 1 minute **(AII)**. Treatment of water with iodine or chlorine might not be as effective as boiling and will not eradicate *Cryptosporidia*, but can be used when boiling is not practical **(BIII)**.

Preventing First Episode of Disease

HIV-infected children aged ≤5 years should receive the Hib conjugate vaccine **(AII)**. Clinicians and other health care providers should consider use of Hib vaccine among HIV-infected children >5 years old who have not previously received Hib vaccine *[30]* **(AIII)**. For these older children, two doses of any conjugate Hib vaccine, administered at least 1 to 2 months apart, can be used *[90]* **(AIII)**.

HIV-infected children aged 2 to 59 months should receive the heptavalent pneumococcal conjugate vaccine (PCV) **(AII)**. A four-dose series of PCV is recommended for routine administration to infants at ages 2, 4, 6, and 12 to 15 months; previously unvaccinated infants and children aged 7 to 23 months are recommended to receive two to three doses depending on age at the time of first vaccination *[37]*. Incompletely vaccinated children aged 24 to 59 months should receive two doses of PCV ≥8 weeks apart.

Children who previously received three PCV doses need only one additional dose. Additionally, children aged >2 years also should receive the 23-valent pneumococcal polysaccharide vaccine (PPV) (≥2 months after their last PCV dose), with a single revaccination with PPV 3 to 5 years later if the child is aged ≤10 years or after 5 years if the child is aged >10 years **(CIII)** *[91]* (Figures 1 and 2). Data are limited regarding efficacy of PCV among children aged ≥5 years and adults who are at high risk for pneumococcal infection. Administering PCV to older children with high-risk conditions (including HIV-infected children) is not contraindicated. One study reported that 5-valent pneumococcal conjugate vaccine is immunogenic among HIV-infected children aged 2 to 9 years *[91]*. A multicenter study of pneumococcal immunization in a group of HIV-infected children not vaccinated with PCV in infancy demonstrated the safety and immunogenicity of two doses of PCV followed by one dose of PPV for HAART-treated, HIV-infected children aged 2 to 19 years (including some who had previously received PPV) *[92]*. 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% vs 85%, respectively), the incidence of invasive pneumococcal disease was substantially decreased among HIV-infected vaccine recipients *[63]*.

HIV-infected children are likely at increased risk for meningococcal disease, although not to the extent that they are at risk for invasive *S. pneumoniae* infection. Although the efficacy of conjugated meningococcal vaccine (MCV4) and meningococcal polysaccharide vaccine (MPSV4) among HIV-infected patients is unknown, HIV infection is not a contraindication to receiving these vaccines *[30]* **(CIII)**. Since 2005, conjugated meningococcal vaccine has been recommended for all children at 11 to 12 years of age. In June 2007, the ACIP recommended that all unvaccinated adolescents aged 13 to 18 years should also be vaccinated *[44]*. A multicenter safety and immunogenicity trial of conjugated meningococcal vaccine in HIV-infected 11 to 24 year olds is currently under way. In addition, it is recommended that children who are at high risk of meningococcal disease on the basis of other conditions (e.g., terminal complement deficiencies, anatomic or functional asplenia) receive MCV4 if aged 2 to 6 years **(BIII)** *[41]*. Although the efficacy of MCV4 and MPSV4 among HIV-infected children is unknown, because patients with HIV are likely at increased risk for meningococcal disease, HIV-infected children that do not fit into the above groups may elect to be vaccinated. Revaccination with MCV4 is indicated for children who had been vaccinated 3 years or more previously with the MPSV4 vaccine.

Since influenza increases the risk of secondary bacterial respiratory infections *[93]*, following guidelines for influenza prevention can be expected to reduce the risk of serious bacterial infections in HIV-infected children (See Figures 1 and 2) **(BIII)**.

To prevent serious bacterial infections among HIV-infected children who have hypogammaglobulinemia (IgG <400 mg/dL), clinicians should use IVIG **(AI)**. In the pre-HAART era, IVIG was effective in preventing serious bacterial infections in symptomatic HIV-infected children *[54]*, but this effect was most clearly demonstrated only in those not receiving daily trimethoprim/sulfamethoxazole (TMP-SMX) for PCP prophylaxis *[55]*. Thus, IVIG is no longer recommended for primary prevention of serious bacterial infections in HIV-infected children unless hypogammaglobulinemia is present or functional antibody deficiency demonstrated by either poor specific antibody titers or recurrent bacterial infections **(CII)**.

TMP-SMX administered daily for PCP prophylaxis is effective in reducing the rate of serious bacterial infections (predominantly respiratory) in HIV-infected children without access to HAART *[55, 94]* **(AII)**. Atovaquone combined with azithromycin, which provides prophylaxis for MAC as well as PCP, has been shown in HIV-infected children to be as effective as TMP-SMX for the prevention of serious bacterial infections and is similarly tolerated *[95]*. However, indiscriminate use of antibiotics (when not indicated for PCP or MAC prophylaxis or other specific reasons) might promote development of drug-resistant organisms. Thus, antibiotic prophylaxis is not recommended to be prescribed solely for primary prevention of serious bacterial infections **(DIII)**.

In developing countries, where endemic deficiency of vitamin A and zinc is common, supplementation with vitamin A and zinc conferred additional protection against bacterial diarrhea and/or pneumonia in HIV-infected children *[96, 97]*. However, in the United States, while attention to good nutrition including standard daily multivitamins is an important component of care for HIV-infected children, additional vitamin supplementation above the recommended daily amounts is not recommended **(DIII)**.

Discontinuing Primary Prophylaxis

A clinical trial, PACTG 1008, demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved immune reconstitution (CD4 >15%) while receiving antiretroviral therapy did not result in excessive rates of serious bacterial infections *[46]*.

Treatment Recommendations

Treatment of Disease

The principles of treatment of serious bacterial infections are the same in HIV-infected and -uninfected children. Collection of specimens for microbiologic studies should be obtained prior to initiation of antibiotic treatment. However, in patients with suspected serious bacterial infections, therapy should be administered empirically and promptly without waiting for results of such studies; therapy can be adjusted once culture results become available. The local prevalence of resistance to common infectious agents (i.e., penicillin-resistant *S. pneumoniae* and MRSA) 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 subsequent therapy based on the results of susceptibility testing **(AII)**.

HIV-infected children whose immune systems are not seriously compromised (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 or cefotaxime is reasonable until culture results are available *[85, 98]* **(AIII)**. The addition of azithromycin can be considered for hospitalized patients with pneumonia to treat other common community-acquired pneumonia pathogens (*Mycoplasma pneumoniae, C. pneumoniae*). If MRSA is suspected or there is a high prevalence (e.g., >10%) of MRSA in the community, clindamycin or vancomycin can be added (choice based on local susceptibility patterns) *[99, 100]*. Neutropenic children should also be treated with an anti-pseudomonal drug such as ceftazidime or imipenem, with consideration of adding an aminoglycoside if infection with *Pseudomonas* spp. is thought likely. 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)**.

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, which has anti-*Pseudomonas* activity, and vancomycin to cover MRSA **(AIII)**. Factors such as response to therapy, clinical status, identification of pathogen, and need for ongoing vascular access will determine the need and timing of catheter removal.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

The response to appropriate antibiotic therapy should be similar in HIV-infected and -uninfected individuals, with a clinical response generally observed within 2 to 3 days after initiation of appropriate

antibiotics; radiologic improvement in patients with pneumonia may lag behind clinical response. Fatal hemolytic reactions to ceftriaxone in HIV-infected children with prior ceftriaxone treatment have been reported *[101]*. While HIV-infected adults experience high rates of adverse and even treatment-limiting reactions to TMP-SMX, serious adverse reactions to TMP-SMX in HIV-infected children appear to be much less of a problem *[102]*.

An IRIS has not been described in association with treatment of bacterial infections in children.

Management of Treatment Failure

The type of bacteria isolated and the antibiotic drug susceptibility pattern should guide changes in antibiotic regimen. Failure of treatment of a serious bacterial infection in an HIV-infected child should prompt consideration that the bacterial pathogen is resistant to the antibiotic therapy; consideration that there is a nonbacterial cause of the pneumonia (e.g., TB, PCP), meningitis (e.g., cryptococcus or TB), catheter-related infection (e.g., *Candida* spp.), or other serious infection; or consideration that there might be a sequestered focus of infection (e.g., an undrained occult abscess) **(AIII)**.

Prevention of Recurrence

Status of immunization against Hib, pneumococcus, meningococcus, and influenza should be reviewed and updated, according to the recommendations outlined in the section **Preventing First Episode of Disease** (see **Figures 1 and 2**) **(AI)**.

TMP-SMX, administered daily for PCP prophylaxis, and azithromycin or atovaquone-azithromycin, administered for MAC prophylaxis, may also reduce the incidence of drug-sensitive serious bacterial infections in children with recurrent serious bacterial infections. While administration of antibiotic chemoprophylaxis to HIV-infected children who have frequent recurrences of serious bacterial infections may be considered, caution is required when using antibiotics solely for preventing the recurrence of serious bacterial infections because of the potential for development of drug-resistant microorganisms and drug toxicity. In rare situations in which antibiotic prophylaxis is not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis **(AI)**.

Discontinuing Secondary Prophylaxis

As noted earlier, PACTG 1008 demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved immune reconstitution (CD4 >15%) while receiving antiretroviral therapy did not result in excessive rates of serious bacterial infections *[46]*.

Bartonellosis

Epidemiology

Bartonella is a genus of facultative intracellular bacteria including 21 species, only a few of which have been implicated as human pathogens *[103-105]*. Of these, *Bartonella henselae* and *Bartonella quintana* cause a spectrum of diseases specifically in immunocompromised hosts, such as those infected with HIV *[106, 107]*. These diseases include bacillary angiomatosis and bacillary peliosis. Immunocompromised individuals are also susceptible to *Bartonella*-associated bacteremia and dissemination to other organ systems. Complications of *Bartonella* infection are relatively uncommon in the pediatric HIV-infected population *[4]*, although complications seen in adult immunocompromised hosts can also occur in immunocompromised children with AIDS. *Bartonella* infections involve an intra-erythrocytic phase that appears to provide a protective niche for the bartonellae leading to persistent and often relapsing infection, particularly in immunocompromised individuals *[103]*. A feature of infections with the genus *Bartonella* is the ability of the bacteria to cause either acute or chronic infection with either vascular proliferative or suppurative manifestations, dependent on the immune status of the patient *[103]*.

B. henselae is typically associated with cat-scratch disease in the general population. Most cases of cat-scratch disease occur in patients aged <20 years *[108]*. A study examining the epidemiology of cat-scratch disease in the United States estimated that 437 pediatric hospitalizations associated with cat-scratch disease occurred among children aged <18 years during the year 2000, giving a national hospitalization rate of 0.6 per 100,000 children aged <18 years and 0.86 per 100,000 children aged <5 years *[109]*. Data on the epidemiology of infection with *Bartonella* spp. in HIV-infected children are lacking.

The household cat is a major vector for transmission of *B. henselae* to humans. While transmission of *B. henselae* from cat to cat appears to be facilitated by cat fleas, data do not suggest that *B. henselae* is efficiently transmitted from cats to humans by fleas *[110]*. More than 90% of patients with cat-scratch disease have a history of recent contact with cats, often kittens *[108]*, and cat scratches or bites *[111]* have been implicated as the principal modes of cat-to-human transmission. Kittens (<1 year of age) are more likely to have *B. henselae* bacteremia, to have high levels of bacteremia, and to scratch than adult cats. Despite the evidence against fleaborne cat-to-human transmission, researchers acknowledge that the potential for such transmission exists and requires further investigation *[110]*. Eradication of flea infestation is important in prevention of transmission because contamination of cat claws or of a scratch wound with infected flea feces is a possible mechanism for infecting humans *[110]*. Infection occurs more often during the autumn and winter *[108, 111-113]*.

B. quintana is globally distributed. The vector for *B. quintana* is the human body louse. Outbreaks of trench fever have been associated with poor sanitation and personal hygiene, which may predispose individuals to the human body louse *[105]*.

Clinical Manifestations

The clinical manifestations of *B. henselae* infection are in large part determined by the host's immune response; localized disease (e.g., focal suppurative regional lymphadenopathy such as in typical cat-scratch disease) appears most commonly in patients with an intact immune system, whereas systemic infection appears more commonly in immunocompromised patients, although systemic disease has also been reported among otherwise normal children *[114, 115]*. Clinical manifestations of *B. henselae* and *B. quintana* specific to HIV-infected and other immunocompromised patients include bacillary angiomatosis and bacillary peliosis.

Bacillary angiomatosis is a rare disorder that occurs almost entirely in severely immunocompromised hosts *[116, 117]*. It is a vascular proliferative disease that has been reported most often in HIV-infected adults with severe immunosuppression with a median CD4 count of <50 cells/mm^3 in a majority of case studies of HIV-infected adults *[107, 118]*. The disease is characterized by cutaneous and subcutaneous angiomatous papules; the lesions of this disease can be confused with KS. Lesions are often papular and red with smooth or eroded surfaces; they are vascular and bleed if traumatized. Nodules may be observed in the subcutaneous tissue and can erode through the skin. It may less frequently involve organs other than the skin.

Bacillary peliosis is characterized by angiomatous masses in visceral organs; it mainly occurs in severely immunocompromised patients with HIV infection. It is a vasoproliferative condition that contains blood-filled cystic spaces. The organ that is most commonly affected is the liver (i.e., peliosis hepatis), but the disease can also involve bone marrow, lymph nodes, lungs, and CNS *[119-121]*.

Immunocompromised patients who are infected with *B. henselae* or *B. quintana* can also present with persisting or relapsing fever with bacteremia and should be considered in the differential diagnosis of fever of unknown origin in immunocompromised children with late stage AIDS *[122]*. Dissemination to almost all organ systems has been described, including bone (e.g., osteomyelitis), heart (e.g., subacute endocarditis), and CNS (e.g., encephalopathy, seizures, neuroretinitis, transverse myelitis) *[123]*. Most patients with visceral involvement have nonspecific systemic symptoms including fever, chills, night sweats, anorexia and weight loss, abdominal pain, nausea, vomiting, and diarrhea.

Diagnosis

Bartonella species are small, gram-negative bacilli. In cases of bacillary angiomatosis and bacillary peliosis, diagnosis is usually made through biopsy with a characteristic histologic picture; clusters of organisms can be demonstrated with Warthin-Starry silver stain of affected tissue. The organisms can be isolated with difficulty from blood or tissue culture using enriched agar; they have been isolated more successfully from specimens taken from patients with bacillary angiomatosis and peliosis than from patients with typical cat-scratch disease *[106]*. *B. henselae*, similar to other *Bartonella* species, is a fastidious, slow-growing organism; in most cases colonies first appear after 9 to 40 days; therefore incubation for up to 6 weeks is recommended *[123]*.

Serologic tests such as indirect fluorescent antibody (IFA) test and enzyme immunoassay (EIA) are also available. The IFA test is available at many commercial laboratories and state public health laboratories and through CDC *[108]*. Unfortunately, cross-reactivity among *Bartonella* species and other bacteria, such as *Chlamydia psittaci [114]*, is common, and serologic tests do not accurately distinguish among them. Additionally, the sensitivity of currently available IFA tests is lower in immunocompromised than in immune competent patients; 25% of HIV-infected *Bartonella* culture-positive patients never develop anti-*Bartonella* antibodies *[120]*.

The most sensitive method of diagnosis is with PCR testing of clinical specimens; different procedures have been developed that can discriminate among different species of *Bartonella [124, 125]*. PCR assays are available in some commercial and research laboratories.

Prevention Recommendations

Preventing Exposure

Prevention of bartonellosis should focus on reducing exposure to vectors of the disease, i.e., the body louse (for *B. quintana*) and cats and cat fleas (for *B. henselae*). Control of cat flea infestation and avoidance of cat scratches are therefore critical strategies for prevention of *B. henselae* infections in HIV-

infected persons. To avoid exposure to *B. quintana*, HIV-infected patients should avoid and treat infestation with body lice.

Individuals with HIV infection, specifically those with severe immunosuppression, should consider the potential risks of cat ownership; risks of cat ownership for HIV-infected children should be discussed with caretakers. If a decision is made to acquire a cat, cats <1 year of age should be avoided *[108, 122]* **(BII)**. HIV-infected persons should avoid playing roughly with cats and kittens to minimize scratches and bites and should promptly wash sites of contact if they are scratched or bitten **(BIII)** *[108]*. Also, cats should not be allowed to lick open wounds or cuts **(BIII)**. No evidence indicates any benefit from routine culturing or serologic testing of cats for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats *[108]* **(DII)**.

Preventing First Episode of Disease

No evidence supports the use of chemoprophylaxis for bartonellosis, such as following a cat scratch **(CIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Management of typical cat-scratch disease in immunocompetent patients is mainly supportive because the disease is usually self-limited and resolves spontaneously in 2 to 4 months. Enlarged, painful lymph nodes may need to be aspirated. Cat-scratch disease typically does not usually respond to antibiotic therapy; it is thought that the localized clinical manifestations of the disease may be due to an immunologic reaction in the lymph nodes with few viable *Bartonella* present by the time a biopsy is performed *[103, 126]*. In one double-blind, placebo-controlled study in a small number (N=29) of immunocompetent older children and adults with uncomplicated cat-scratch disease, azithromycin resulted in a more rapid decrease in initial lymph node volume by sonography, although there was no difference in clinical outcome *[127]*. Thus, antibiotic treatment is generally not recommended for uncomplicated, localized disease.

The *in vitro* and *in vivo* antibiotic susceptibilities of *Bartonella* do not correlate well for a number of antibiotics; for example, penicillin demonstrates *in vitro* activity but has no *in vivo* efficacy *[103, 114]*. Although no systematic clinical trials have been done, antibiotic treatment of bacillary angiomatosis and peliosis hepatitis is recommended on the basis of reported experience in clinical case series as severe, progressive, and disseminated disease can occur, and without appropriate therapy, systemic spread can occur and involve virtually any organ *[103, 107]*. Guidelines for treatment of *Bartonella* infections have been published *[103]*.

The drug of choice for treatment of systemic bartonellosis is erythromycin or doxycycline *[103, 120]* **(AII)**. Clarithromycin or azithromycin treatment has been associated with clinical response, and either of these can be an alternative for *Bartonella* treatment **(BIII)** *[128]*.

For patients with severe disease, intravenous administration may be needed initially **(AIII)** *[129]*. Therapy should be given for 3 months for cutaneous bacillary angiomatosis and 4 months for bacillary peliosis, CNS disease, osteomyelitis, or severe infections, as treatment must be of sufficient duration to prevent relapse *[103, 122]* **(AII)**. Combination therapy with the addition of rifampin to either erythromycin or doxycycline is recommended for immunocompromised patients with acute, life-threatening infections *[103, 122]* **(BIII)**. Because doxycycline has better CNS penetration than

erythromycin, the combination of doxycycline and rifampin is preferred for treatment of patients with CNS *Bartonella* infection, including retinitis **(AIII)**.

Endocarditis is most commonly caused by *B. quintana*, followed by *B. hensalae*, but has also been linked to infection with *B.elizabethae*, *B. vinsonii* subps. *Berkhoffii*, *B. vinsonii* subps. *Arupensis*, *B. kohlerae*, and *B. alsatica [130]*. For suspected (but culture-negative) *Bartonella* endocarditis, 14 days of aminoglycoside treatment **(AII)** accompanied by ceftriaxone (to adequately treat other potential causes of culture-negative endocarditis) with or without doxycycline for 6 weeks is recommended **(BII)** *[103]*. For documented culture-positive *Bartonella* endocarditis, doxycycline for 6 weeks plus gentamicin intravenously for the first 14 days is recommended **(BII)** *[103, 108]*.

Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(DII)** *[131]*. Quinolones and TMP-SMX have variable *in vitro* activity and an inconsistent clinical response in case reports *[114]*; as a result, they are not recommended for treatment **(DIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Response to treatment can be dramatic in immunocompromised patients. Cutaneous bacillary angiomatosis skin lesions usually improve and resolve after a month of treatment. Bacillary peliosis responds more slowly than cutaneous angiomatosis, but hepatic lesions should improve after several months of therapy.

Some immunocompromised patients develop a potentially life-threatening Jarisch-Herxheimer-like reaction within hours after institution of antibiotic therapy, and immunocompromised patients with severe respiratory or cardiovascular compromise should be monitored carefully following institution of therapy *[103, 106]*.

No cases of *Bartonella*-associated IRIS have been reported.

Management of Treatment Failure

In immunocompromised patients who relapse, retreatment should be continued for 4 to 6 months; repeated relapses should be treated indefinitely *[127]* **(AIII)**. Among patients who fail to respond to initial treatment, one or more of the second-line regimens should be considered **(AIII)**.

Prevention of Recurrence

Relapses in bone and skin have been reported and are more common when antibiotics are given for a shorter duration (<3 months), especially in severely immunocompromised patients. In the setting of an immunocompromised HIV-infected adult experiencing relapse, long-term suppression of infection with doxycycline or a macrolide is recommended as long as the CD4 cell count is <200 cells/mm^3 **(AIII)**. Although there are no data for HIV-infected children, it seems reasonable that similar recommendations should be followed.

Discontinuing Secondary Prophylaxis

No specific data regarding the discontinuation of secondary prophylaxis are available at this time.

Syphilis

Epidemiology

Treponema pallidum can be transmitted from mother to child at any stage of pregnancy or during delivery. Among women with untreated primary, secondary, early latent, or late latent syphilis at delivery, approximately 30%, 60%, 40%, and 7% of infants, respectively, will be infected. Treatment of the mother for syphilis ≥30 days before delivery is required for effective *in utero* treatment.

Congenital syphilis has been reported despite adequate maternal treatment. Factors that contribute to treatment failure include maternal stage of syphilis (early stage), advancing gestational age at treatment, higher Venereal Disease Research Laboratory (VDRL) titers at treatment and delivery, and short interval from treatment to delivery (<30 days) *[132, 133]*. In 2005, the rate of congenital syphilis declined to 8 cases per 100,000 live births *[134]*, down from 13.4 cases per 100,000 live births in 2000 and 27.8 cases per 100,000 live births in 1997. Overall, there has been a 74% decrease in cases of congenital syphilis since 1996. The continuing decline in the rate of congenital syphilis likely reflects the substantial reduction in the rate of primary and secondary syphilis among women that has occurred during the last decade.

Drug use during pregnancy, particularly the use of cocaine, has been associated with an increased risk for maternal syphilis and congenital infection *[135]*. Similarly, HIV-infected women have a higher prevalence of untreated or inadequately treated syphilis during pregnancy that places their newborns at higher risk for having congenital syphilis *[136]*. Mother-to-child HIV transmission might be increased when concurrent syphilis coinfection is present during pregnancy *[136-138]*; transmission does not appear to be increased if the mother's syphilis is effectively treated before pregnancy *[136]*.

Although approximately two-thirds of the sexually transmitted diseases (STDs) diagnosed annually in the United States occur among persons aged <24 years, such individuals account for <25% of early syphilis cases. Nevertheless, the prevalence and incidence of syphilis among HIV-infected youth and of HIV infection among youth with syphilis are appreciable; in a study of 320 HIV-infected and -uninfected adolescents aged 12 to 19 years in the United States, the prevalence of syphilis was 9% among HIV-infected female youth and 6% among HIV-infected male youth *[139]*. In a meta-analysis of 30 studies, the median HIV seroprevalence among persons infected with syphilis in the United States was 15.7% (27.5% among men and 12.4% among women with syphilis) *[140]*.

Clinical Manifestations

Untreated early syphilis during pregnancy can lead to spontaneous abortion, stillbirth, hydrops fetalis, preterm delivery, and perinatal death in up to 40% of pregnancies *[141]*. Among children with congenital syphilis, there are two characteristic syndromes of clinical disease that are referred to as early and late congenital syphilis. *Early congenital syphilis* refers to those clinical manifestations that appear within the first 2 years of age. Those features that occur after 2 years are designated as *late congenital syphilis*.

At birth, infected infants may manifest such signs as hepatosplenomegaly, jaundice, mucocutaneous lesions (e.g., skin rash, nasal discharge, mucous patches, condyloma lata), lymphadenopathy, pseudoparalysis of an extremity, anemia, thrombocytopenia, pneumonia, and skeletal lesions (e.g., osteochondritis, periostitis, or osteitis). In a study of 148 infants born to mothers with untreated or inadequately treated syphilis, 47% had clinical, radiographic, or conventional laboratory findings consistent with a diagnosis of congenital syphilis, and 44% had a positive rabbit infectivity test, PCR assay, or IgM immunoblot of serum, blood, or CSF *[142]*. However, as many as 60% of infants with congenital syphilis do not have any clinical signs at birth *[143]*. If untreated, these "asymptomatic"

infants may develop clinically apparent disease in the ensuing 3 weeks to 6 months. In addition to those findings described above, fever, nephrotic syndrome, and hypopituitarism may occur.

The manifestations of acquired syphilis in older children and adolescents are similar to those of adults (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*. HIV-infected persons with acquired early syphilis might be at increased risk for neurological complications and uveitis and have higher rates of treatment failure *[144]*.

Diagnosis

The standard serologic tests for syphilis in adults are based on the measurement of IgG antibody. Because IgG antibody in the infant reflects transplacental passively transferred antibody from the mother, interpretation of reactive serologic tests for syphilis among infants is difficult. Therefore, the diagnosis of neonatal congenital syphilis depends on a combination of results from physical, laboratory, radiographic, and direct microscopic examinations.

All infants born to women with reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal test (e.g., VDRL slide test, rapid plasma reagin [RPR], or the automated reagin test). Testing should be performed on neonatal serum because of the potential for maternal blood contamination of the umbilical cord blood specimens. Performing specific treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and *T. pallidum* particle agglutination (TP-PA) test, is not necessary for evaluation of congenital syphilis in the neonate. No commercially available IgM test is recommended for diagnostic use. (Note: Some laboratories use treponemal tests, such as EIA, for screening, then perform nontreponemal tests on those that are positive *[145]*. However, there is no published experience of such an approach with congenital syphilis.)

Definitive diagnosis of congenital syphilis can be made if *T. pallidum* is detected in umbilical cord, placenta, nasal discharge, or skin lesion material using darkfield microscopic examination or direct fluorescent antibody staining of lesions or body fluids; false-negative results are common. Pathologic examination of placenta and umbilical cord with specific fluorescent antitreponemal antibody staining is recommended.

Evaluation of suspected cases of congenital syphilis should include a careful and complete physical examination. Further evaluation is dependent on maternal treatment history for syphilis, findings on physical examination, and planned infant treatment and may include a complete blood count and differential and platelet count; long bone radiographs; and CSF analysis for VDRL, cell count, and protein. HIV-infected infants might have increased cell counts and protein concentrations even in the absence of neurosyphilis. Other tests should be performed as clinically indicated (e.g., chest radiograph, liver function tests, cranial ultrasound, ophthalmologic examination, and auditory brainstem response).

A proven case of congenital syphilis requires the visualization of spirochetes by darkfield microscopy or fluorescent antibody testing of body fluid(s). Finding that an infant's serum quantitative nontreponemal serologic titer is 4-fold higher than the mother's titer is suggestive of infection but not a criterion in the case definition. A presumptive case of syphilis is defined as an infant born to a mother with untreated or inadequately treated syphilis at delivery, regardless of findings in the infant, or any infant who has a reactive treponemal test result and signs of congenital syphilis on physical examination, laboratory evaluation, long bone radiographs, positive CSF VDRL test, or an abnormal CSF finding without other cause.

For diagnosis of acquired syphilis, a reactive nontreponemal test must be confirmed by a specific treponemal test such as FTA-ABS or TP-PA. Treponemal tests will usually remain positive for life, even

with successful treatment. The prozone phenomenon (a weakly reactive or falsely negative) reaction might occur more frequently in HIV-infected persons *[146]*. Treponemal antibody titers do not correlate with disease activity and should not be used to monitor treatment response. CSF evaluation should be performed among HIV-infected adolescents with acquired syphilis of unknown or <1 year's duration or if they have neurologic or ocular symptoms or signs; many clinicians recommend a CSF examination for all HIV-infected patients with syphilis (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*.

Prevention Recommendations

Preventing Exposure

Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks gestation and at delivery. Moreover, as part of the management of pregnant women who have syphilis, information concerning treatment of sex partners should be obtained to assess the risk for reinfection. Routine screening of newborn sera or umbilical cord blood is not recommended. Serologic testing of the mother's serum is preferred rather than testing of the infant's serum because the serologic tests performed on infant serum can be nonreactive if the mother's serologic test result is of low titer or the mother was infected late in pregnancy. No HIV-exposed infant should leave the hospital unless the maternal serologic status has been documented at least once during pregnancy, and at delivery in communities and populations in which the risk for congenital syphilis is high *[147, 148]*.

Acquired Syphilis

Primary prevention of syphilis includes routine discussion of sexual behaviors that may place persons at risk for infection. Providers should discuss risk reduction messages that are client centered and provide specific actions that can reduce the risk for STD acquisition and HIV transmission *[149-151]*.

Routine serologic screening for syphilis is recommended at least annually for all sexually active HIV-infected persons, with more frequent screening (3 to 6 months) dependent on individual risk behaviors (e.g., multiple partners, sex in conjunction with illicit drug use, methamphetamine use, or partners that participate in such activities) *[152]*. The occurrence of syphilis in an HIV-infected person is an indication of high-risk behavior and should prompt intensified counseling messages and consideration of referral for behavioral intervention. Persons undergoing screening or treatment for syphilis should also be evaluated for all common STDs *[153]*.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Penicillin remains the treatment of choice for syphilis, congenital or acquired, regardless of HIV status.

Congenital 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 *[154]*.

Infants should be treated for congenital syphilis if the mother has (1) untreated or inadequately treated syphilis (including treatment with erythromycin or any other nonpenicillin regimen), (2) no documentation of having received treatment, (3) received treatment ≤4 weeks before delivery, (4) been treated with penicillin but nontreponemal antibody titer did not decrease by 4-fold, or (5) ≥4-fold increase in nontreponemal antibody titer suggesting relapse or reinfection *[153]* **(AII)**. Infants should be treated regardless of maternal treatment history if there is 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 ≥4-fold greater than maternal titer *[153]* **(AII)**.

Treatment for proven or highly probable congenital syphilis (i.e., infants with findings, symptoms, or whose titers are ≥4-fold greater than maternal titer) is aqueous crystalline penicillin G at a dose of 100,000 – 150,000 units/kg/day, administered as 50,000 units/kg/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 50,000 units/kg/dose intravenously every 4 to 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 (IM) daily in a single dose for 10 days **(BII)**. However, aqueous penicillin G is preferred because of its higher penetration into the CSF. There are no published reports of treatment failures with ampicillin or studies of the effectiveness of ampicillin for the treatment of congenital syphilis.

Asymptomatic infants born to mothers who have had adequate treatment and response to therapy, and with a normal physical examination and CSF findings, but who have a serum quantitative nontreponemal serologic titer that is <4-fold higher than maternal titer might be treated with a single dose of benzathine penicillin G 50,000 units/kg/dose IM 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 G because physical examination and laboratory test results cannot definitively exclude congenital syphilis in all cases **(BII)**.

Acquired Syphilis

Acquired syphilis in children is treated with a single dose of benzathine penicillin G 50,000 units/kg IM (up to the adult dose of 2.4 million units) for early stage disease (e.g., primary, secondary, and early latent disease) **(AII)**. For late latent disease, three doses of benzathine penicillin G 50,000 units/kg should be administered IM once weekly for three 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 *[153]* **(EIII)**. Neurosyphilis should be treated with aqueous penicillin G 200,000 – 300,000 units/kg intravenously per day in divided doses given every 4 to 6 hours (maximum dose: 18 – 24 million units/day) for 10 to 14 days **(AII)**. See ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults*** for dosing recommendations for older HIV-infected adolescents with acquired syphilis *[16]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

All seroreactive infants (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2 to 3 months until the test becomes nonreactive or the titer has decreased 4-fold **(AIII)**. Nontreponemal antibody titers should decline by age 3 months and should be nonreactive by age 6 months if the infant was not infected (i.e., if the reactive test result was caused by passive transfer of maternal IgG antibody) or was infected but adequately treated. The serologic response after therapy might be slower for infants treated after the

neonatal period. It is not known if children with congenital syphilis who also are HIV infected take longer to become nonreactive and require retreatment.

Treponemal tests should not be used to evaluate treatment response because the results for an infected child can remain positive despite effective therapy. Passively transferred maternal treponemal antibodies can be present in an infant until age 15 months. A reactive treponemal test after age 18 months is diagnostic of congenital syphilis. If the nontreponemal test is nonreactive at this time, no further evaluation or treatment is necessary. If the nontreponemal test is reactive at age 18 months, the infant should be fully (re)evaluated and treated for congenital syphilis **(BIII)**.

Infants whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis.

HIV-infected children and adolescents with acquired early syphilis (i.e., primary, secondary, early latent) 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 4-fold by 6 to 12 months after successful therapy, with examination of CSF and retreatment strongly considered in the absence of such a decline. For syphilis of longer duration, follow-up is indicated at 6, 12, and 24 months; a 4-fold decline should be expected by 12 to 24 months. If initial CSF examination demonstrated a pleocytosis, repeat lumbar puncture should be conducted at 6 months after therapy and then every 6 months until the cell count is normal. Follow-up CSF examinations can also be used to evaluate changes in the VDRL-CSF or CSF protein levels after therapy, but changes in these parameters occur more slowly than changes in CSF cell counts. Data from HIV-infected adults with neurosyphilis suggest that CSF abnormalities might persist for extended periods and close clinical follow-up is warranted *[144]*.

There are no reported cases of syphilis (congenital or acquired) in an HIV-infected child manifesting as IRIS and only very rare reports of syphilis-associated IRIS in adults (primarily syphilitic ocular inflammatory disease) *[155]*.

Management of Treatment Failure

After treatment of congenital syphilis, children with increasing or stable nontreponemal titers at age 6 to 12 months or those who are seropostive with any titer at 18 months should be evaluated (e.g., including a CSF examination) and considered for retreatment with a 10-day course of parenteral penicillin **(AIII)**.

The management of failures of treatment of acquired syphilis in older children and adolescents is identical to that in adults (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*. Retreatment of patients with early-stage syphilis should be considered for those who (1) do not experience at least a 4-fold decrease in serum nontreponemal test titers 6 to 12 months after therapy, (2) have a sustained 4-fold increase in serum nontreponemal test titers after an initial reduction post-treatment, or (3) have persistent or recurring clinical signs or symptoms of disease **(BIII)**. If CSF examination does not confirm the diagnosis of neurosyphilis, such patients should receive 2.4 million units IM benzathine penicillin G administered at 1-week intervals for 3 weeks **(BIII)**. Certain specialists have also recommended a course of aqueous penicillin G IV or procaine penicillin IM plus probenicid (as described above for treatment of neurosyphilis) for all patients with treatment failure, although data to support this recommendation are lacking **(CIII)**. If titers fail to respond appropriately after retreatment, the value of repeat CSF evaluation or retreatment has not been established.

Patients with late latent syphilis should be retreated if they (1) have clinical signs or symptoms of syphilis, (2) have a 4-fold increase in serum nontreponemal test titer, or (3) experience an inadequate

serologic response (i.e., a <4-fold decline in nontreponemal test titer) within 12 to 24 months of therapy if initial titer was high (e.g., >1:32) **(BIII)**. Such patients should have a repeat CSF examination performed. If the repeat CSF examination is consistent with CNS involvement, retreatment should follow the neurosyphilis recommendations **(AIII)**; those without a CSF profile indicating CNS disease should receive a repeat course of benzathine penicillin, 2.4 million units IM weekly for 3 weeks **(BIII)**, although certain specialists recommend following the neurosyphilis recommendations in this setting as well **(CIII)**.

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

Prevention of Recurrence

No recommendations have been developed for secondary prophylaxis or chronic maintenance therapy for syphilis in HIV-infected children.

Discontinuing Secondary Prophylaxis

Not applicable.

MYCOBACTERIAL INFECTIONS:
Mycobacterium tuberculosis

Epidemiology

In 2006, of the 13,779 cases of TB disease reported in the United States, 807 (6%) occurred in children aged younger than 15 years *[156]*. Overall, for the period 1993 – 2001, 12.9% of adults with TB were reported to be coinfected with HIV, compared with 1.1% of all childhood TB cases *[157]*. However, the actual rate of HIV coinfection in U.S. children with TB is unknown because of the very low rate of HIV testing in this population.

Numerous studies have documented the increased risk of TB in HIV-infected adults. Domestic and international studies have documented a similar increased risk for TB disease among HIV-infected children *[158-161]*. Unlike other AIDS-related OIs, CD4 cell count is not a sufficient indicator of increased risk for TB disease in HIV-infected children. Congenital TB is rare but has been reported among children born to HIV-infected women with TB disease *[162, 163]*.

Children with TB disease almost always became infected by contact with an adult in their daily environment, and their disease represents the progression of primary infection rather than the reactivation disease commonly observed among adults *[164]*. Identification and treatment of the source patient and evaluation of all exposed members of the household are particularly important because other secondary TB cases and latent infections with *M. tuberculosis* are often found. All confirmed and suspected TB cases should be reported to state and local health departments, who will assist in contact evaluation.

Disease due to *Mycobacterium bovis* has reemerged among children in New York City in recent years, and *M. bovis* is a frequent cause of TB disease in children in San Diego County *[165, 166]*. Recent cases have been associated with the consumption of unpasteurized fresh cheese from Mexico *[165]*. The majority of human *M. bovis* cases are attributable to consumption of unpasteurized milk or its products, and exposure to this pathogen in the United States is unlikely except from privately imported products. However, human-to-human airborne transmission from pulmonary cases has been confirmed, and its relevance might be increased by HIV infection. The distinction between *M. tuberculosis* and *M. bovis* is important for determining the source of infection for a child who has TB disease and for selecting a treatment regimen: almost all *M. bovis* isolates are resistant to pyrazinamide.

Disease due to BCG, an attenuated version of *M. bovis*, has been reported in HIV-infected children who were vaccinated with BCG at birth *[167]*. IRIS due to BCG has also been reported among children initiating HAART *[22, 167]*.

Internationally, drug resistance is a growing obstacle to controlling TB, but in the United States, effective public health approaches to prevention and treatment have reduced the rates of drug resistance. Data from U.S. surveillance during 1993 – 2001 among children with TB indicate that *M. tuberculosis* with resistance to any of the first-line anti-TB drugs was identified in 15.2% of children with culture-positive *M. tuberculosis*, with higher rates among foreign-born children (19.2%) than U.S.-born children (14.1%) *[157]*. Multidrug-resistant TB (MDR TB) is unusual among U.S.-born TB patients. The prevalence of multidrug resistance (e.g., at least isoniazid and rifampin) was higher in foreign-born children (2.8%) than in U.S.-born children (1.4%) with TB. However, the fraction of adult TB patients in the United States who are foreign born is increasing, and they are a potential source of drug-resistant infection for their U.S.-born children.

Clinical Manifestations

Children aged younger than 4 years and all HIV-infected children are more likely to develop active disease once infected. In general, the clinical features of TB disease in HIV-infected children are similar to those among children without HIV infection, although the disease is usually more severe *[168, 169]* and can be difficult to differentiate from illnesses caused by other OIs. Pulmonary involvement is evident in most cases and can be characterized by localized alveolar consolidation, pneumonitis, and hilar and mediastinal adenopathy. Concomitant atelectasis might result from hilar adenopathy compressing bronchi or from endobronchial granulomas. HIV-infected children with TB are more likely to be symptomatic, with fever and cough, and have atypical findings, such as multilobar infiltrates and diffuse interstitial disease. Rapidly progressive disease, including meningitis or mycobacterial sepsis, can be seen without obvious pulmonary findings. Both HIV infection and young age increase the rate of miliary disease and TB meningitis. Older HIV-infected children and adolescents have clinical features more similar to those seen in HIV-infected adults, with the typical apical lung infiltrates and late cavitation *[170]*. Approximately 25% of pediatric non-HIV TB cases include extrapulmonary disease as a sole or concomitant site, and HIV-infected children may have an even higher rate. The more common sites of extrapulmonary disease among children include lymph nodes, hematogenous (miliary), CNS, bone, pericardium, and peritoneum *[168, 171-173]*.

Diagnosis

The cornerstone of diagnostic methods for latent TB infection (LTBI) is the tuberculin skin test (TST), administered by the Mantoux method. Because children with HIV infection are at high risk for TB, annual testing of this population is recommended to diagnose LTBI **(AIII)**. Among persons with HIV infection, ≥5 mm of induration is considered a positive (diagnostic) reaction. However, among immunocompetent children with active TB disease, approximately 10% have a negative TST result, and HIV-infected children with TB disease are even more likely to have a negative result. Therefore, a negative TST result should never be relied upon for excluding the possibility of TB. The use of control skin antigens at the time of purified protein derivative (PPD) testing to assess for cutaneous anergy is of uncertain value and no longer routinely recommended **(DII)**.

Sensitivity to tuberculin is reduced by severe viral infections such as wild-type measles. As a precaution, skin testing that is scheduled around the time of live-virus vaccination should be done at the same time or delayed until 6 weeks after vaccination, to avoid any potentially suppressed sensitivity to the skin test **(AIII)**.

Two-step skin testing is used for detecting boosted sensitivity to tuberculin in health care workers and others at the time of entry into a serial testing program for occupational TB exposure. The utility and predictive value of two-step testing have not been assessed for children (with or without HIV infection), and its usage is not recommended **(DIII)**.

Recently, *ex vivo* assays that determine IFN-γ release from lymphocytes after stimulation by highly specific synthetic *M. tuberculosis* antigens have been developed for diagnosing infection *[174]*. QuantiFERON®-TB (QFT) Gold and QuantiFERON®-TB Gold In-Tube (Cellestis Limited) are now Food and Drug Administration (FDA) approved and are available in the United States. Newer tests, including the T-SPOT.*TB* assay (Oxford Immunotec), are awaiting final FDA approval. These tests were shown to be more specific than the TST in a number of studies among adults, especially those who are BCG vaccinated. However, as with the TST, these tests are less sensitive in HIV-infected adults with advanced immune suppression *[175]*. In addition, limited data suggest these tests, particularly QuantiFERON, might have less sensitivity for diagnosing infection in young children *[176]*. At present, their routine use for finding LTBI or diagnosing TB disease in HIV-infected children is not recommended because of the uncertainty about test sensitivity *[174]* **(DIII)**.

Patients with a positive test for LTBI should undergo chest radiography and clinical evaluation to rule out active disease. Diagnostic microbiologic methods for TB consist of microscopic visualization of acid-fast bacilli (AFB) from clinical specimens, nucleic-acid amplification for direct detection in clinical specimens, the isolation in culture of the organism, drug susceptibility testing, and genotyping. Although acid-fast stained sputum smears are positive in 50% – 70% of adults with pulmonary TB, young children with TB disease rarely produce sputum voluntarily and typically have a low bacterial load *[177]*. Smear results are frequently negative even among older children who are able to expectorate and provide a sample *[157]*. Nevertheless, a positive smear result usually is indicative of mycobacteria, although it does not differentiate *M. tuberculosis* from other mycobacterial species. Mycobacterial culture improves sensitivity and permits species identification and drug susceptibility testing and genotyping. Confirming *M. tuberculosis* infection with a culture can have greater significance for HIV-infected children because of the difficulties of the differential diagnosis. Therefore, culture for mycobacteria should be performed on all samples that are sent for microscopy. Bronchoscopy will increase the likelihood of obtaining a positive smear and culture. Obtaining early morning gastric aspirates for AFB stain and culture is the diagnostic method of choice in children unable to produce sputum. A standardized protocol that includes testing of three samples obtained separately may improve the yield from gastric aspirates to 50% *[178]*. Others have shown the potential utility of induced sputum *[179, 180]* and nasopharyngeal aspirates *[181]* for obtaining diagnostic specimens from children in the outpatient setting.

Two commercial nucleic acid amplification kits are FDA approved for direct detection of *M. tuberculosis* in sputum samples with positive smear-microscopy results. One of the methods is also approved for sputa with negative microscopy. A positive result from these methods provides immediate confirmation of the diagnosis. However, when these tests are used for other specimens, such as gastric aspirates or cerebrospinal fluid, sensitivity and specificity have been disappointing *[182-184]*. These assays provide adjunctive, but not primary, diagnostic evaluation of children with TB, because a negative result does not rule out TB as a diagnostic possibility and a positive result does not account for drug susceptibility testing. However, it might be useful in establishing the diagnosis of TB among HIV-infected children with unexplained pulmonary disease, when both culture and tuberculin skin tests may be falsely negative.

Because of the difficulty in obtaining a specimen for bacteriological diagnosis of TB disease among children, the evidence for the diagnosis often involves linking the child to an adult with confirmed TB together with a positive TST and an abnormal radiograph or physical examination in the child *[177]*. A high index of suspicion is important. Suspicion for and diagnosis of TB in HIV-infected children is further complicated by the frequent presence of pre-existing or coincidental fever, pulmonary symptoms, and radiographic abnormalities (e.g., chronic lymphoid interstitial pneumonitis or coincident pulmonary bacterial infection) and the decreased sensitivity of TST in this population. Strenuous efforts should be made to obtain diagnostic specimens (three each of sputum or gastric aspirate specimens or induced sputum) whenever a presumptive diagnosis of TB is made or when it is suspected.

Because many children do not have culture-proven TB, and source cases may have a delay in the diagnosis of drug resistance, MDR TB should be suspected in children with TB disease in the following situations *[90, 185-187]*:

• A child who is a close contact of an MDR TB patient.

• A child who is a contact of a TB patient who died while on treatment when there are reasons to suspect that the disease was MDR TB (i.e., the deceased patient had been a contact of another MDR TB case, had poor adherence to treatment or had received >2 courses of antituberculosis treatment).

• Children with bacteriologically proven TB who are not responding to first-line drugs given with direct observation.

• Children exposed to source cases that remain smear or culture positive after 2 months of directly observed first-line antituberculosis therapy

• Children born in or exposed to residents of countries or regions with a high prevalence of drug-resistant TB.

Antimycobacterial drug susceptibility testing should be performed on the initial *M. tuberculosis* isolate and on subsequent isolates if treatment failure or relapse is suspected; the radiometric culture system has been adapted to perform rapid sensitivity testing. Before obtaining results of susceptibility testing or if an organism has not been isolated from specimens from the child, the antimycobacterial drug susceptibility of the *M. tuberculosis* isolate from and treatment history of the source case can be used to define the probable drug susceptibility of the child's organism and to design the empiric therapeutic regimen for the child.

Prevention Recommendations

Preventing Exposure

Children most commonly are infected with *M. tuberculosis* from exposure in their immediate environment, usually the household. HIV-infected children may have family members dually infected with HIV and TB. Homeless children or those exposed to institutional settings (including prolonged hospitalization) may be at increased risk. Risk factors of close contacts of HIV-infected children (e.g., homelessness, incarceration, exposure to institutional settings) should also be considered. BCG vaccine is not routinely administered in the United States and should not be administered to HIV-infected infants and children because of its potential to cause disseminated disease **(EII)** *[188]*.

Preventing First Episode of Disease

In the United States, where TB exposure is uncommon and BCG is not routinely administered, HIV-infected infants and children should have a TST (5-TU PPD) at 3 months of age, and children should be tested at the time of HIV diagnosis. HIV-infected children should be retested at least once per year **(AIII)**.

HIV-infected infants and children should be treated for LTBI if they have a positive TST **(AI)** or exposure to a person who has contagious TB (after excluding active TB disease in the infant or child and regardless of the child's TST results) **(AII)**. The duration of preventive therapy for children should be 9 months and the preferred regimen is isoniazid (10 – 15 mg/kg/day **[AII]** or 20 – 30 mg/kg twice weekly **[BII]**). Liver function tests should be performed prior to starting isoniazid **(AII)** for HIV-infected children and further monitoring should be performed if the baseline tests are abnormal, the patient has chronic liver disease, or medications include other potentially hepatotoxic drugs, such as acetaminophen and some antiretroviral drugs. If isoniazid resistance is known or suspected in the source case, rifampin for 4 to 6 months is recommended **(BII)**. A 2-month regimen of rifampin and pyrazinamide was never recommended for children and now is not recommended for any age group because of an increased risk of severe and fatal hepatotoxicity **(EII)**. Children exposed to drug-resistant strains should be managed by an experienced clinician and the regimen should be individualized based on what is known about the source case susceptibility pattern and treatment history.

A randomized, double-blind, controlled trial of isoniazid in HIV-infected children in South Africa was halted when isoniazid administered daily or twice weekly (according to the cotrimoxazole schedule) was found to have a benefit in reducing mortality (hazard ratio 0.46; 95% CI 0.22 – 0.95, p=0.015) *[189]*. These findings were found across all ages and CDC HIV disease classification and were independent of TST result, although the study may not have been adequately powered to detect these differences. These results suggest that HIV-infected children in extremely high TB burden areas may benefit from isoniazid preventive therapy irrespective of any known exposure to TB, but this approach is not currently recommended in the United States due to the low prevalence of TB **(DII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Empiric TB therapy should be started in HIV-infected infants and children in whom the diagnosis is suspected and continued until the diagnosis is definitively ruled out **(AII)**. The use of directly observed therapy (DOT) decreases the rates of relapse, treatment failures, and drug resistance and is recommended for treatment of all children and adolescents with TB in the United States **(AII)**. DOT means that a trained worker, and not a family member, watches the patient ingest each dose of medication. The principles for treatment of TB in the HIV-infected child are the same as for the HIV-uninfected child. However, the treatment of TB in an HIV-infected child is complicated by antiretroviral drug interactions with the rifamycins and overlapping toxicities caused by antiretroviral drugs and TB medications. Rifampin is a potent inducer of the CYP3A family of enzymes. Rifabutin is a less potent inducer but is a substrate of this enzyme system.

Doses and side effects of TB medications are included in the tables. In the absence of concurrent HAART, initial empiric treatment of TB disease should generally consist of a four-drug regimen (isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin) **(AI)**. For the first 2 months of treatment, DOT should be administered daily (intensive phase). Modifications of therapy should be based on susceptibility testing, if possible. The drug susceptibility pattern from the isolate of the adult source case can guide treatment in cases when an isolate is not available from the child. If the organism is found to be susceptible to isoniazid, rifampin, and pyrazinamide during the 2-month intensive phase of therapy, ethambutol (or streptomycin) can be discontinued and the intensive phase completed using three drugs **(AI)**.

Following the 2-month intensive phase, for treatment of *M. tuberculosis* known to be sensitive to isoniazid and rifampin, therapy is continued with isoniazid and rifampin as DOT two to three times weekly (continuation phase) **(AI)**; daily therapy during the continuation phase is also acceptable **(AI)**. Children with severe immunosuppression should only receive 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; thus twice-weekly dosing should only be considered for children without immune suppression (e.g., CD4 >15%, or >100 cells/mm^3 if >6 years of age) **(CIII)** *[190]*. Ethionamide can be used as an alternative to ethambutol in cases of TB meningitis **(CIII)** because ethionamide has better CNS penetration than ethambutol.

For HIV-infected children with active pulmonary TB disease, the minimum recommended duration of antituberculous drug treatment is 6 months, but some experts recommend up to 9 months **(AIII)** *[89]*; for children with extrapulmonary disease involving the bones or joints, CNS, or miliary disease, the minimum recommended duration of treatment is 12 months *[90, 191]* **(AIII)**. These recommendations assume that the organism is susceptible to the medications, that adherence to the regimen has been assured by DOT, and that the child has had a clinical and microbiologic response to therapy.

For HIV-infected children who are diagnosed with TB disease, anti-TB treatment must be started immediately **(AIII)**. However, treatment of TB in the setting of HAART is complicated by unfavorable pharmacokinetic interactions and overlapping toxicities and should be managed by a specialist with expertise in treating both these conditions **(AIII)**. Issues to consider when treating both conditions include (1) the critical role played by rifampin because of its potent bactericidal properties; (2) rifampin's potent

induction of the CYP3A enzyme system that precludes treatment with all protease inhibitors (PIs) but may allow treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs); (3) the CYP3A induction by rifabutin is less potent but there may still be a need for dose adjustments of both rifabutin and possibly the PIs, although there are minimal data in children; (4) overlapping toxicities; and (5) the challenges of adherence to a medication regimen that may include ≥7 drugs.

Given these challenges, some experts have argued that the role of rifamycins for the treatment of TB is so important, the effect of the rifamycins on PI (and possibly NNRTI) levels is so unpredictable, and the subsequent risk of HIV resistance is so great that, in an antiretroviral-naïve child, deferral of HAART until completion of TB therapy should be considered. Others recommend that treatment of TB in an antiretroviral-naïve HIV-infected child should be initiated 2 to 8 weeks before initiating antiretroviral medications to improve adherence and better differentiate potential side effects. Which option to consider must take into account clinical factors, such as clinical stage of HIV, immune status of the child, age, ability to adhere to complicated drug regimens, and other comorbid conditions. For children with severe immune compromise, earlier initiation of HAART (e.g., 2 weeks after antimycobacterial therapy is started) may be advisable (although there is a risk of IRIS), while more delayed initiation of HAART might be considered for children with higher CD4 counts **(BII)**.

The choice of antiretroviral regimen in an HIV-infected child being treated for TB disease is complex, and advice should be obtained from an expert in the treatment of these two diseases. Starting antiretroviral therapy with an NNRTI-based rather than a PI-based regimen is preferred because NNRTI regimens have fewer interactions with rifampin-based TB therapy **(BII)**. However, NNRTIs are also metabolized via the CYP3A enzyme system and efavirenz and nevirapine are both CYP3A4 enzyme inducers. Efavirenz is the preferred NNRTI in HIV-infected children aged >3 years, while nevirapine is the preferred NNRTI for children aged <3 years, as the dosing for efavirenz in younger children has not been defined and there is no pediatric formulation. There are currently no data in children on the pharmacokinetics of either drug in combination with rifampin to make specific recommendations regarding potential need for an increase in dose of the NNRTI. If a PI is used, a ritonavir-boosted PI such as lopinavir/ritonavir is required. There are no pharmacokinetic data to address whether additional ritonavir boosting is needed in children receiving rifampin and lopinavir/ritonavir-based regimens.

For children already receiving antiretroviral therapy who have had TB diagnosed, the issues are equally complicated and similar considerations must be taken into account. Treatment for TB must be started immediately **(AIII)** and 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. These recommendations are limited because of the paucity of data on the optimal dosing of medications to treat TB in children, especially in children who are HIV infected. Guidelines and recommendations exist for dose adjustments necessary in adults when treated with rifabutin and PIs, but the absence of data precludes extrapolating these to HIV-infected children being treated for TB. Consultation with an expert in pediatric HIV and TB infection is recommended. More data are needed on the pharmacokinetics of anti-TB medications in both HIV-infected and -uninfected children.

For treatment of drug-resistant TB, a minimum of three drugs should be administered, including two or more bactericidal drugs to which the isolate is susceptible **(AII)**. Regimens can include three to six drugs with varying levels of activity. Children infected with MDR 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 to 12 months of a rifampin- or rifabutin-containing regimen (e.g., rifampin, pyrazinamide, and ethambutol) **(BII)**. 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 should be administered, followed by an additional continuation phase of isoniazid, pyrazinamide, and

ethambutol to complete a minimum of a 12- to 18-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 to 3 months for patients with severe disease **(BIII)**. When the strain is resistant to isoniazid and rifampin (i.e., MDR TB), therapeutic regimens must be individualized based on the resistance pattern, treatment history of the patient or the source case, relative activities of the drugs, extent of disease, and any comorbid conditions. The duration of therapy should be at least 12 months, and usually longer. In children who are smear or culture positive at treatment initiation, therapy should generally be continue for 18 to 24 months after smear and culture conversion. Among children with paucibacillary disease (e.g., smear and culture negative), therapy may be of shorter duration but should be ≥12 months *[90, 192]*.

Extensively drug-resistant tuberculosis (XDR TB) has emerged globally as an important new threat, particularly in persons infected with HIV *[193]*. XDR TB is a strain of TB resistant to isoniazid and rifampin (which defined MDR TB) plus additional resistance to any fluoroquinolone and ≥1 of 3 injectable drugs: capreomycin, kanamycin, and amikacin *[194]*. Of the 49 cases of XDR TB identified in the United States from 1993 to 2006, 1 (3%) occurred in a child aged <15 years *[194]*. However, this number possibly underestimates the burden in children, as many TB cases in children are not culture positive and thus a definitive diagnosis of drug resistance (including MDR or XDR) is not possible. Children with suspected or confirmed XDR TB should be managed in consultation with an expert, as such cases are associated with rapid disease progression in the presence of HIV coinfection and a high mortality rate.

Adjunctive treatment with corticosteroids is indicated for children with TB 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)**. Anti-TB therapy must be administered concomitantly. Most experts use 1 – 2 mg/kg/day of prednisone or its equivalent for 6 to 8 weeks.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Monthly monitoring of clinical and bacteriologic response to therapy is important **(AII)**. For children with pulmonary TB, chest radiographs should be obtained after 2 to 3 months of therapy to evaluate response **(AIII)**. Hilar adenopathy might persist for as long as 2 to 3 years despite successful anti-TB 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.

Common side effects associated with TB medications are listed in Table 5. Isoniazid is available as syrup, but some specialists advise against using it because the syrup is unstable and frequently causes diarrhea. Gastric upset during the initial weeks of isoniazid treatment occurs frequently and can often be avoided by having some food in the stomach when isoniazid is given. Hepatotoxicity is the most common serious adverse effect. It includes subclinical hepatic enzyme elevation, which usually resolves spontaneously while treatment is continued and clinical hepatitis that usually resolves when the drug is discontinued; it rarely progresses to hepatic failure, but the likelihood of life-threatening liver damage is increased by continuing isoniazid in spite of hepatitis symptoms. Hepatotoxicity is less frequent in children than in adults, but no age group is risk free. 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 *[191, 195]*. However, the rate of hepatotoxicity might be greater in children taking multiple hepatotoxic medications and those who have HIV infection. Pyridoxine (150 mg/day) is recommended for all symptomatic HIV-infected children treated with isoniazid **(AII)**.

HIV-infected children on anti-TB medications should have liver enzymes obtained at baseline and monthly thereafter **(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 to 3 times the upper limit of normal) do not require discontinuation of drugs if other findings are normal **(AII)**, but they do require more frequent rechecks until they resolve—as often as weekly.

The most ominous toxicity associated with ethambutol 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 – 25 mg/kg among children with normal renal function *[192]*. Assessments of renal function, ophthalmoscopy, and (if possible) visual acuity and color vision should be performed before starting ethambutol and monitored regularly during treatment with the agent **(AIII)**. Hypothyroidism has been associated with ethionamide and periodic (e.g., monthly) monitoring of thyroid hormone serum concentrations is recommended with its use **(AIII)**.

Major adverse effects of aminoglycoside drugs are oto- and nephrotoxicity. Periodic audiometry, monitoring of vestibular function (as possible), and blood urea nitrogen and creatinine are recommended **(AIII)**.

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 **(AIII)**. Coadministration of pyridoxine (150 mg/day) with cycloserine is recommended **(AII)**. Thiacetazone can cause severe and often fatal reactions among HIV-infected children, including severe rash and aplastic anemia, and should not be used **(EIII)**.

An IRIS in patients receiving anti-TB therapy in the setting of HAART has been reported in HIV-infected adults *[196-198]*. New onset of systemic symptoms, especially high fever, expanding CNS lesions, and worsening adenopathy, pulmonary infiltrates, or pleural effusions have been reported in HIV-infected adults in the setting of HAART up to several months after starting TB therapy. These cases have also been reported in children *[22, 191, 199]* and should be suspected in children with advanced immune suppression who initiate HAART and subsequently develop new symptoms.

This IRIS occurs in two common clinical scenarios. First, patients with occult TB prior to initiating HAART may have unmasking of their TB by immune recovery following antiretroviral drug initiation. This is referred to as "unmasking IRIS" or incident TB-IRIS, usually occurs within the first 3 to 6 months after initiation of HAART, and the infectious pathogen is typically detectable. Second, IRIS can also occur as paradoxical exacerbation of TB after initiating HAART in a patient already receiving anti-TB treatment, through a clinical recrudescence of a successfully treated infection or symptomatic relapse despite initial clinical improvement and continued microbiologic treatment success; this is referred to as "paradoxical IRIS." In paradoxical IRIS, persons are already on TB treatment at the time of antiretroviral treatment initiation, and treatment failure due to microbial resistance or poor adherence must be ruled out.

The literature on IRIS in children consists largely of case reports and small series, so it is not clear whether IRIS occurs more often in children than in adults. Persons with mild-to-moderate symptoms of IRIS have been treated symptomatically with nonsteroidal anti-inflammatory drugs while continuing anti-TB and HIV therapies. In certain cases, use of systemic corticosteroids for 1 to 2 weeks results in improvement while continuing to receive TB/HIV therapies *[196-198]* **(CIII)**. However, no controlled trials of the use of corticosteroids have been published. TB therapy should not be discontinued.

Management of Treatment Failure

Most children with TB respond well to medical therapy. If response is not good, then an evaluation that includes assessment of adherence to therapy, drug absorption, and drug resistance should be carried out. Mycobacterial culture, drug susceptibility testing, and antimycobacterial drug levels should be performed whenever possible. Drug resistance should be suspected in any child who fails to convert their smear or culture after 2 months of anti-TB therapy as DOT. In the absence of bacteriologic confirmation of disease in the first place, failure should be suspected in children who do not have resolution of clinical symptoms, including failure to gain weight, and who have radiographic evidence of disease progression on therapy. As described above, drug-resistant TB should be managed in consultation with an expert.

Prevention of Recurrence

Risk of recurrence is rare in children with drug-susceptible TB who are treated under direct observation. If TB recurs, the child is at high risk of drug resistance and should be managed accordingly.

Chronic suppressive therapy for a patient who has successfully completed a recommended regimen of treatment for TB is unnecessary **(DII)**. Secondary prophylaxis is not recommended for children who have had a prior episode of TB. However, HIV-infected children who were treated for LTBI or TB and who come into contact with contagious TB again should be treated for presumed latent infection, after diagnostic evalution excludes current disease.

Discontinuing Secondary Prophylaxis

Not applicable.

Mycobacterium avium Complex Disease

Epidemiology

Mycobacterium avium complex (MAC) refers to multiple related species of nontuberculous mycobacteria (e.g., *M. avium*, *M. intracellulare*, *M. paratuberculosis*) that are widely distributed in the environment. Comprehensive guidelines on the diagnosis, prevention, and treatment of nontuberculous mycobacterial (NTM) diseases were recently published *[200]*. These guidelines highlight the tremendous advances in laboratory methods in mycobacteriology that have expanded the number of known NTM species from 50 in 1997 to more than 125.

MAC was the second most common OI among children with HIV infection in the United States after PCP in the pre-HAART era, but its incidence has greatly decreased from 1.3 – 1.8 episodes per 100 person-years in the pre-HAART era to 0.14 – 0.2 episodes per 100 person-years in the HAART era *[3, 4]*. MAC is ubiquitous in the environment and is presumably acquired by routine exposures through inhalation, ingestion, or inoculation *[201]*. A recent study of adults and children found that soil exposure along with Black race and birth outside the United States were associated with MAC infection in a population-based study in Florida *[202]*. Respiratory and GI colonization can act as portals of entry that can lead to disseminated infection *[203]*.

MAC can appear as isolated lymphadenitis among HIV-infected children. Disseminated infection with MAC in pediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4 count, and it is a complication of advanced immunologic deterioration among HIV-infected children *[201, 204, 205]*. Disseminated MAC can occur at higher CD4 cell counts among younger HIV-infected children than among older children or adults, especially among HIV-infected children aged <2 years.

Clinical Manifestations

Respiratory symptoms are uncommon among HIV-infected children with disseminated MAC, and isolated pulmonary disease is rare. Early symptoms can be minimal and may precede mycobacteremia by several weeks. Symptoms commonly associated with disseminated MAC infection among children include persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue, persistent diarrhea, and persistent or recurrent abdominal pain. Lymphadenopathy, hepatomegaly, and splenomegaly can be found. Laboratory abnormalities include anemia, leukopenia, and thrombocytopenia. Serum chemistries are usually normal, although some children may have elevations in alkaline phosphatase or lactate dehydrogenase. It should be noted that these signs and symptoms are also relatively common among HIV-infected children with advanced immunosuppression in the absence of disseminated MAC.

Diagnosis

Procedures used to diagnose MAC in children are the same as used in HIV-infected adults (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*. Definitive diagnosis is accomplished by isolation of the organism from the blood or from biopsy specimens from normally sterile sites (e.g., bone marrow, lymph node, or other tissues). Multiple mycobacterial blood cultures over time may be required to yield a positive result. Recovery of organisms from blood is enhanced by use of a radiometric broth medium or lysis-centrifugation culture technique.

Histology demonstrating macrophage-containing acid-fast bacilli strongly indicates MAC in a patient with typical signs and symptoms, but culture is essential to differentiate NTM from *M. tuberculosis* to determine which NTM is the cause of infection and to perform drug susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended **(BIII)**. The Bactec

method for radiometric susceptibility testing can be used. Susceptibility thresholds for clarithromycin are minimal inhibitory concentrations (MIC) of ≥32 ug/mL and an MIC of ≥256 ug/mL for azithromycin *[206]*.

Prevention Recommendations

Preventing Exposure

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance. Person-to-person transmission is not believed to be common.

Preventing First Episode of Disease

The most effective way to prevent disseminated MAC among HIV-infected children is to preserve immune function through use of effective antiretroviral therapy. HIV-infected children who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the following CD4 count thresholds **(AII)** *[207, 208]*:

- children aged ≥6 years: <50 cells/mm^3;
- children aged 2 to 5 years: <75 cells/mm^3;
- children aged 1 to 2 years: <500 cells/mm^3; and
- children aged <1 year: <750 cells/mm^3.

For the same reasons that clarithromycin and azithromycin are the preferred prophylactic agents for adults, either one should be considered for prophylaxis in children **(AII)**; oral suspensions of both agents are commercially available in the United States. Before prophylaxis is initiated, evaluation for the presence of disseminated MAC disease should be carried out, which should usually include obtaining a blood culture for MAC **(AIII)**.

Although detecting MAC in stool or respiratory tract may precede disseminated disease, no available data support initiating prophylaxis in patients with detectable organisms at these sites in the absence of a positive blood culture for MAC. Therefore, routine screening of respiratory or GI specimens for MAC is not recommended **(DIII)**.

Discontinuing Primary Prophylaxis

Primary prophylaxis for MAC can be safely discontinued in HIV-infected adults who respond to antiretroviral therapy with an increase in CD4 count based upon both randomized controlled trials and observational data. In a study of discontinuing OI prophylaxis among HIV-infected children whose CD4 percentages were ≥20% for those aged >6 years and ≥25 % for those aged 2 to 6 years, 63 HIV-infected children discontinued MAC prophylaxis, and no MAC events were observed during ≥2 years of follow-up *[46]*. Based on these findings and data from studies in adults, primary prophylaxis can be discontinued in HIV-infected children aged >2 years receiving stable HAART for ≥6 months who experience sustained (>3 months) CD4 cell recovery well above the age-specific target for initiation of prophylaxis (e.g., similar to adults, >100 cells/mm^3 for children aged ≥6 years and >200 cells/mm^3 for children aged 2 to 5 years) **(BII)**.

Treatment Recommendations

Treatment of 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 two drugs is recommended to prevent or delay the emergence of resistance **(AI)**. Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.

Improved immunologic status is important for control of disseminated MAC disease; potent antiretroviral therapy should be initiated among children with MAC disease who are antiretroviral naïve. However, the optimal time to start HAART in this situation is unknown; many experts treat MAC with antimycobacterial therapy for 2 weeks before starting HAART to try to minimize the occurrence of IRIS, although whether this makes a difference is unknown **(CIII)**. For children already receiving HAART, it should be continued and optimized unless drug interactions preclude the safe concomitant use of antiretroviral and antimycobacterial drugs.

Doses and side effects of MAC medications are included in the tables. Initial empiric therapy should include two or more drugs **(AI)**: clarithromycin or azithromycin plus ethambutol. Some experts use clarithromycin as the preferred first agent **(AI),** reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern **(AII)**. PIs can increase and efavirenz can decrease clarithromycin levels but no data are available to recommend dose adjustments for pediatric patients. Azithromycin is not metabolized by the cytochrome P450 (CYP450) system; therefore, it can be used without concern for significant drug interactions with PIs and NNRTIs.

Because a study in adult patients demonstrated a survival benefit with the addition of rifabutin to clarithromycin plus ethambutol, some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen **(CI)**; however, drug interactions should be checked carefully, and more intensive toxicity monitoring might be warranted if such drugs are given concomitantly **(AIII)**. Because rifabutin increases CYP450 activity that leads to increased clearance of other drugs (e.g., PIs and NNRTIs), and increased toxicity might be observed with concomitant administration of drugs, other experts recommend against the use of this third agent in children **(CIII)**. Guidelines and recommendations exist for dose adjustments necessary in adults who are treated with rifabutin and PIs, but the absence of pediatric data precludes extrapolating these to HIV-infected children being treated for disseminated MAC. There is no pediatric formulation of rifabutin, although the drug can be administered mixed with foods such as applesauce. Limited safety data are available from use in 22 HIV-infected children (median age, 9 years) who received rifabutin in combination with two or more other antimycobacterial drugs for treatment of MAC for periods of 1 to 183 weeks; doses ranged from 4 to 18.5 mg/kg/dose, and reported adverse effects were similar to those reported in adults *[209]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Most patients demonstrate substantial clinical improvement during the first 4 to 6 weeks of therapy. A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiation of antimycobacterial therapy in patients who fail to have a clinical response to their initial treatment regimen. Improvement in fever can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response might be delayed and elimination of the organism from the blood might require up to 12 weeks of effective therapy.

An IRIS in patients receiving MAC therapy in the setting of HAART has been reported among HIV-infected adults and children *[210-212]*. New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal lymphadenitis (cervical, thoracic, or abdominal) associated with pre-existing but relatively asymptomatic MAC infection has been seen after starting HAART. Before initiation of HAART among HIV-infected children with low CD4 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 *[211]*. Children with moderate symptoms of IRIS 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)**.

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations of liver transaminase levels or hypersensitivity reactions. The major toxicity associated with ethambutol 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 – 25 mg/kg among children with normal renal function. Assessments of renal function, ophthalmoscopy, and (if possible) visual acuity and color vision should be performed before starting ethambutol and monitored regularly during treatment with the agent **(AIII)**.

Patients receiving clarithromycin plus rifabutin should be observed for the rifabutin-related development of leucopenia, uveitis, polyarthralgias, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some HIV-infected children receiving rifabutin as part of a multidrug regimen for MAC *[209]*.

Management of Treatment Failure

Treatment failure is defined by the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment. Repeat susceptibility testing of MAC isolates is recommended in this setting, and a new multidrug regimen of two or more drugs not previously used and to which the isolate is susceptible should be administered **(AIII)**. Drugs that should be considered under this scenario include rifabutin, amikacin, and a quinolone. In HIV-infected adults, based on data from treating MAC in HIV-uninfected patients, an injectable agent such as amikacin or streptomycin should be considered **(CIII)** *[200]*. Because dosing of these agents in pediatrics can be problematic, treatment for drug-resistant disseminated MAC should be carried out with input from an expert in this disease **(AIII)**. Optimization of antiretroviral therapy is an especially important adjunct to treatment of patients who have failed initial MAC therapy.

Prevention of Recurrence

Children with a history of disseminated MAC should be administered lifelong prophylaxis to prevent recurrence **(AII)**.

Discontinuing Secondary Prophylaxis

Based upon immune reconstitution data in adults and data in children discontinuing primary prophylaxis, some experts recommend discontinuation of secondary prophylaxis in HIV-infected children aged >2 years who have completed a course of ≥12 months of treatment for MAC, remain asymptomatic with respect to signs and symptoms of MAC, and are receiving stable HAART who experience sustained (≥6 months) CD4 cell recovery well above the age-specific target for initiation of primary prophylaxis (e.g., similar to adults, >100 cells/mm^3 for children aged >6 years and >200 cells/mm^3 for children aged 2 to 6 years) **(CIII)**. Secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

FUNGAL INFECTIONS:
Aspergillosis

Epidemiology

Aspergillus species are ubiquitous molds that are widespread in soil, growing on plants and decomposing organic materials *[213]* that are infrequent pathogens in HIV-infected children. The most common species causing aspergillosis are *A. fumigatus*, followed by *A. flavus [214, 215]*. Aspergillosis is a rare but often lethal infection in pediatric AIDS patients. The estimated incidence of invasive aspergillosis in pediatric AIDS patients was 1.5% – 3% prior to widespread use of HAART *[216-218]*. It is thought to be a much less prevalent infection in the post-HAART era. Specific risk factors include low CD4 count, neutropenia, corticosteroid use, concurrent malignancy with chemotherapy, broad spectrum antibiotic exposure, previous pneumonia and respiratory OIs, and HIV-related phagocytic impairment *[216, 219-223]*.

Clinical Manifestations

Invasive pulmonary aspergillosis is the most common presentation among HIV-infected children *[222, 224, 225]*. Other manifestations include necrotizing tracheobronchitis; pseudomembranous tracheobronchitis; and involvement of CNS, cutaneous, sinus, middle ear, and mastoid *[216-220, 226]*. Disseminated aspergillosis is rare but has been described in previous studies *[216, 227]*. Invasive pulmonary aspergillosis is commonly associated with fever, cough, dyspnea, and pleuritic pain. Acute respiratory distress and wheezing or fungal cast production can occur with necrotizing tracheobronchitis, and stridor with laryngotracheitis *[213, 216, 224]*. *Aspergillus* infections of the CNS manifest as single or multiple cerebral abscesses, meningitis, an epidural abscess, or a subarachnoid hemorrhage *[213]*. Cutaneous aspergillosis is typically associated with contaminated adhesive tapes and arm boards used to secure intravenous devices *[213, 216]*.

Diagnosis

The organism usually is not recoverable from blood (except *A. terreus*) but is isolated readily from lung, sinus, brain, and skin biopsy specimens *[216, 221, 228]*. A definitive diagnosis requires the presence of relevant clinical signs and symptoms and the histopathologic demonstration of organisms in biopsy specimens obtained from involved sites (e.g., liver or brain). A presumptive diagnosis of respiratory tract disease can be made in the absence of a tissue biopsy if *Aspergillus* species are recovered from a respiratory sample, compatible signs and symptoms are present, and no alternative diagnosis is identified *[90]*. A serologic assay for detection of galactomannan, a molecule found in the cell wall of *Aspergillus* species, is available commercially but has not been evaluated widely in infants and children. In addition, the assay is also found to have higher false-positive results in children *[229, 230]*. Therefore, use of galactomannan assays for early detection of aspergillosis is not recommended **(DIII)**.

Radiologic examination plays an important role in diagnosis and follow-up of invasive pulmonary aspergillosis. Chest radiograph demonstrates either a diffuse interstitial pneumonitis or a localized wedge-shaped dense infiltrate representing pulmonary infarction *[213, 216]*. Computed tomography (CT) of the chest may be used to identify the halo sign, a macronodule surrounded by a perimeter of ground-glass opacity, which is an early sign of invasive pulmonary aspergillosis *[231]*. Cavitation and air crescent formation shown in chest CT with an aspergilloma appear more frequently in older children and adults than in younger children *[232-235]*.

Prevention Recommendations

Preventing Exposure

In HIV-infected children who are severely immunosuppressed or neutropenic, considerations for preventing exposure to *Aspergillus* might include excluding plants and flowers from rooms, avoiding food items such as nuts and spices that are often contaminated, and minimizing application of nonsterile biomedical devices and adhesive tape *[213, 236-238]*. Other hospital environmental measures that may be effective in preventing aspergillosis outbreaks include structuring suitable barriers between patient care areas and construction sites; routine cleaning of showerheads, hot water faucets, and air handling systems; repair of faulty air flow; confinement of patients to hospital rooms supplied with sterile laminar airflow (LAF); and installation of high-efficiency particulate air (HEPA) filters *[90, 239-241]*.

Preventing First Episode of Disease

The use of chemoprophylaxis for aspergillosis is not recommended in HIV-infected children because of the low incidence of invasive disease and the unknown efficacy of potential prophylaxis in children, combined with the potential toxicities of likely agents *[242-244]*. Low-dose amphotericin B, itraconazole, or voriconazole prophylaxis has been employed to prevent aspergillosis, with unknown efficacy.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

The recommended treatment for invasive aspergillosis is voriconazole, a second-generation triazole and synthetic derivative of fluconazole *[245-248]*. Adult data have shown voriconazole to be superior to conventional amphotericin B in treatment of aspergillosis and that it is associated with superior survival *[245]* **(AI)**. However, there are only limited data in children.

In immunocompromised children with invasive fungal infection in a compassionate use program of voriconazole, including 42 children with aspergillosis, voriconazole treatment had a complete or partial response in 45% overall, with 43% response in children with aspergillosis *[249, 250]*. The optimal pediatric dose of voriconazole is not yet known. Children require higher doses (on a mg per kg body weight basis) of voriconazole than adults to attain similar serum concentrations. The recommended dose of voriconazole for children is 6 – 8 mg/kg intravenously or 8 mg/kg orally every 12 hours for two doses, followed by 7 mg/kg intravenously or orally twice daily *[251]*. For critically ill patients, the parenteral administration is recommended **(AIII)**. Therapy is continued for ≥12 weeks, but treatment duration should be individualized for each patient based on clinical response *[90]*. Voriconazole has not been studied in HIV-infected children.

Voriconazole is cleared primarily through three key hepatic microsomal CYP450 enzymes, CYP2C19, CYP2C9, and CYP3A4, with most metabolism mediated through CYP2C19 *[252]*. As a result of a point mutation in the gene encoding CYP2C19, some individuals are poor metabolizers and others are extensive metabolizers; about 3% – 5% of white and African human populations are poor metabolizers, while 15% – 20% of Asian populations are poor metabolizers *[247, 252]*. Drug levels can be as much as 4-fold greater in poor metabolizers than in individuals who are homozygous extensive metabolizers. Coadministration of voriconazole with drugs that are potent CYP450 enzyme inducers can significantly reduce voriconazole levels. Voriconazole should be used cautiously with HIV PIs and efavirenz because of potential interactions, and consideration given to therapeutic drug monitoring if used concomitantly **(CIII)**.

Amphotericin B, either conventional or a lipid formulation, is an alternative regimen *[90, 253]* **(AIII)**. The standard amphotericin B deoxycholate dose is 1.0 – 1.5 mg/kg/day. Lipid formulations of amphotericin B allow administration of higher dosage, deliver higher tissue concentrations of drug to reticuloendothelial organs (e.g., lungs, liver, spleen), have fewer infusion-related side effects and less renal toxicity, but are more expensive; dosing of 5 mg/kg/day is recommended.

Surgical excision of a localized invasive lesion may be warranted, especially in sinus aspergillosis, certain cases of pulmonary aspergillosis with impingement on great vessels or pericardium, those with hemoptysis from a single focus, and those with erosion into the pleural space or ribs **(BIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

The main side effects of voriconazole include reversible dose-dependent visual disturbances (increased brightness, blurred vision) in about a third of patients, elevated hepatic transaminases with higher doses, and occasional skin rash *[247]*; as noted earlier, interactions with PIs and efavirenz can be a problem. The primary toxicities of amphotericin B include infusion-related fever/chills and nephrotoxicity.

Patients should be monitored for adverse effects related to antifungal agents, especially amphotericin B. Only one case of aspergillosis-associated IRIS has been described *[254]*.

Management of Treatment Failure

The efficacy of antifungal therapy in invasive aspergillosis has been extremely poor. No data are available to guide recommendations for the management of treatment failure. For patients who had failed treatment or were unable to tolerate voriconazole, amphotericin B should be considered **(BIII)**. Itraconazole for aspergillosis refractory to primary therapy with voriconazole is not recommended due to the similar mechanisms of action and possible cross resistance **(DIII)**.

Caspofungin is approved for adults with invasive aspergillosis who fail to improve or are intolerant of standard therapy, and could be considered for treatment failure in children, although there are limited data on this drug in children**.** In a pharmacokinetic study in 39 children aged 2 to 12 years, dosing on a body surface area basis was recommended over a weight-based dosing scheme; a dose of 50 mg/meter^2 body surface area once daily resulted in area under the curve concentrations similar to exposure in adults receiving the standard dose of 50 mg/day *[255]*. Due to limited bioavailability, caspofungin is only available for intravenous use.

Combination therapy with caspofungin and voriconazole has been studied in a small number of adults and children with invasive aspergillosis *[256-258]*. In the setting of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than the initial regimen may be used **(BIII)** *[256, 258-263]*.

Prevention of Recurrence

For patients with non-HIV-related immunosuppression, continuation of antifungal therapy throughout the duration of immunosuppression seems to be associated with a more favorable outcome in other patient populations *[264]*. However, no data are available in HIV-infected populations, and hence no recommendations can be made for or against secondary prophylaxis **(CIII)**.

Discontinuing Secondary Prophylaxis

Not applicable.

Candida Infections

Epidemiology

The most common fungal infections among HIV-infected children are caused by *Candida* species. Oral thrush and diaper dermatitis occur among 50% – 85% of HIV-infected children. *Candida albicans* is the most common cause of mucosal and esophageal candidiasis. Localized disease caused by *Candida* is characterized by limited tissue invasion to the skin or mucosa. Examples of localized candidiasis include oropharyngeal and esophageal disease; vulvovaginitis; and diaper dermatitis. Once the organism penetrates the mucosal surface and widespread hematogenous dissemination occurs, invasive candidiasis ensues. This can result in candidemia, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease.

Although oropharyngeal candidiasis (OPC) continues to be one of the most frequent OIs in HIV-infected children in the HAART era, seen in 28% of children, the incidence rate (0.93 per 100 child-years) has decreased from the pre-HAART era *[3]*. The incidence of esophageal or tracheobronchial candidiasis has also decreased from a rate of 1.2 per 100 child-years in the pre-HAART era *[1]* to 0.08 per 100 child-years in the HAART era (2001 – 2004) *[1]*. Candida esophagitis continues to be seen in children who are not responding to antiretroviral therapy *[265, 266]*. Children who develop esophageal candidiasis despite HAART therapy may be less likely to have typical symptoms (e.g., odynophagia and retrosternal pain) or have concomitant OPC *[267]*; in the pre-HAART era, concomitant OPC occurred in 94% of children with candida esophagitis *[265]*. Risk factors for esophageal candidiasis include low CD4 count (<100 cells/mm^3), high viral load, and neutropenia (<500 cells/mm^3) within 4 weeks of the episode *[1, 3, 265, 266]*.

Disseminated candidiasis is infrequent among HIV-infected children, but *Candida* can disseminate from the esophagus particularly when coinfection with herpes simplex virus (HSV) or CMV is present *[227, 265]*. Candidemia occurs in up to 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or intravenous antibiotics *[266, 268]*. Approximately 50% of reported cases of *Candida* bloodstream infections in HIV-infected children are caused by non-*albicans Candida* species including *C. tropicalis, C. pseudotropicalis, C. parapsilosis, C. glabrata, C. kruse,* and *C. dubliniensis.* In one study of Cambodian HIV-infected children on HAART with candidiasis, more than 75% (7/9) of the isolated *C. glabrata* were resistant to fluconazole and more than 40% (3/7) of the *C. parapsilosis* isolated were resistant to more than three azole agents *[269]*. It is important to note that species-specific epidemiology varies widely by geographic location and hospital. A substantial number of children who develop candidemia have received systemically absorbed oral antifungal azole compounds (e.g., ketoconazole or fluconazole) for control of oral and esophageal candidiasis *[266]*. Early detection and treatment of candidemia can decrease mortality. Overall mortality was 90% in one study in children who had >14 days of fever and symptoms before diagnosis of disseminated infection with *Candida* species *[227]*.

Clinical Manifestations

Clinical manifestations of OPC are variable and include pseudomembranous (thrush), erythematous (atrophic), hyperplastic (hypertrophic), and angular cheilitis. Thrush appears as creamy white curdlike patches with inflamed underlying mucosa that is exposed after removal of the exudate. It can be found on the oropharyngeal mucosa, palate, and tonsils. Erythematous OPC are flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis is composed of raised white plaques appearing on the lower surface of the tongue, palate, and buccal mucosa and cannot be removed. Angular cheilitis occurs as red, fissured lesions in the corners of the mouth.

Esophageal candidiasis often presents with odynophagia, dysphagia, or retrosternal pain, and a substantial number of children, in contrast to adults, experience nausea and vomiting. These symptoms can present as dehydration and weight loss in children. Evidence of OPC can be absent among children with esophageal candidiasis, particularly those receiving HAART.

New onset fever in an HIV-infected child with advanced disease and a central venous catheter is the most common clinical manifestation of candidemia. Renal candidiasis presents with candiduria and ultrasonographically demonstrated renal parenchymal lesions, often without symptoms related to renal disease *[266]*. Candidemia can lead to endogenous endophthalmitis, and ocular examination by an ophthalmologist is warranted in children with bloodstream *Candida* infection.

Diagnosis

Diagnosis of oral candidiasis can be made by a potassium hydroxide preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. For recurrent or refractory OPC, cultures with *in vitro* susceptibility testing can be used to guide antifungal treatment *[270]*.

Esophageal candidiasis has a classic cobblestoning appearance on barium swallow. In refractory symptomatic cases, endoscopy should be performed to rule out other causes of refractory esophagitis (e.g., HSV, CMV, MAC, and azole-resistant *Candida* species). Endoscopy might show few small white raised plaques to elevated confluent plaques with hyperemia and extensive ulceration.

Diagnosis of candidemia is best made with blood cultures using lysis-centrifugation techniques *[266]* or automated broth-based systems *[271]*. When candidemia is present, depending on clinical suspicions, there can be consideration of retinal examination for endophthalmitis, abdominal CT or ultrasound for hepatic or renal involvement, and bone scans for osteomyelitis.

New diagnostic techniques such as the urine D-arabinitol/L-arabinitol ratio *[272]*, serum D-arabinitol/creatinine ratio *[273]*, *Candida* antigen mannan *[274]*, (1-3)-beta-D-Glucan assay *[275]*, and real time PCR *[276]* are promising diagnostic alternatives under development for early diagnosis of invasive candidiasis in children; but none of these assays has been validated for use in children.

Prevention Recommendations

Prevention of Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals, and no measures are available to reduce exposure to these fungi.

Preventing First Episode of Disease

Routine primary prophylaxis of candidiasis among HIV-infected infants and children is not indicated, given the low prevalence of serious *Candida* infections (e.g., esophageal, tracheobronchial, disseminated) in the HAART era and the availability of effective treatment. There are also concerns regarding potential development of resistant *Candida* strains, drug interactions between antifungal agents and antiretrovirals, and the lack of randomized controlled trials in the pediatric population *[277]* **(DIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Oropharyngeal Candidiasis

Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral polyenes (such as nystatin or amphotericin B suspension) *[278]* **(BII)**. Troches should not be used in infants **(DIII)**. 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 *[279]*.

Systemic therapy with one of the oral azoles (e.g., fluconazole, ketoconazole, or itraconazole) is also effective for initial treatment of OPC *[280, 281]*. Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants, is easier to administer to children than the topical therapies, and is the recommended treatment if systemic therapy is used *[280, 282]* **(AI)**.

Itraconazole solution is comparable in efficacy to fluconazole and can also be used to treat OPC, although it is less well tolerated than fluconazole *[283]* **(AI)**. Absorption of itraconazole solution is enhanced by the presence of gastric acid; it should be taken without food when possible. 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. Ketoconazole absorption is also variable, and therefore neither itraconazole capsules nor ketoconazole are recommended for treatment of OPC if fluconazole or itraconazole solutions are available **(DII)**.

Esophageal Disease

Systemic therapy is essential for esophageal disease **(AI)** and should be initiated empirically among HIV-infected children with OPC and esophageal symptoms. In most patients, symptoms should resolve within days of the start of effective therapy. Oral or intravenous fluconazole or oral itraconazole solutions, given for 14 to 21 days, are highly effective for treatment of *Candida* esophagitis *[284]* **(AI)**. As for OPC, ketoconazole and itraconazole capsules are not recommended for treatment because of variable absorption and lower efficacy **(DII)**.

Voriconazole, a newer azole antifungal, or caspofungin, an echinocandin inhibitor of fungal (1,3)-beta-D-glucan synthetase that must be given intravenously due to limited bioavailability, are also effective in treating esophageal candidiasis in HIV-infected adults **(BI)** *[285-287]*, but there is less experience with these drugs in children. Voriconazole has been used in a limited number of children without HIV infection to treat invasive fungal infections, including some with esophageal candidiasis or candidemia *[250, 267]*. Voriconazole was generally initially administered intravenously and changed to oral administration to complete therapy after the child had stabilized. The optimal pediatric dose of voriconazole is not yet known; children require higher doses (on a mg/kg body weight basis) than adults to attain similar serum voriconazole concentrations. The recommended voriconazole dose for children is 6 – 8 mg/kg intravenously or 8 mg/kg orally every 12 hours *[251]*. However, extrapolations from a pharmacokinetic study of voriconazole in immunocompromised children without HIV infection suggests that children may need a dose as high as 11 mg/kg administered every 12 hours to achieve concentrations similar to the adult dose of 4 mg/kg every 12 hours, although doses this high have not been studied *[252]*. A pharmacokinetic study of caspofungin in immunocompromised children aged 2 to 17 years without HIV infection demonstrated that a dose of 50 mg/meter^2 body surface area/day (70 mg/day maximum) provides comparable exposure to that obtained in adults receiving a standard 50-mg daily regimen *[255]*. Because of limited experience with both of these drugs in children, data are insufficient to recommend use of voriconazole or caspofungin as first-line therapy for esophageal or disseminated candidiasis **(CIII)**.

Invasive Disease

Central venous catheters should be removed when feasible in HIV-infected children with candidemia *[266, 270]* **(AII)**.

Conventional amphotericin B (sodium deoxycholate complex) is the drug of choice for most invasive *Candida* infections in children, given once daily intravenously over 1 to 2 hours **(AI)**. In patients with azotemia, hyperkalemia, or who are receiving high doses (>1 mg/kg), a longer infusion time of 3 to 6 hours is recommended *[288]* **(BIII)**. In children with life-threatening disease, the target daily dose of amphotericin B should be administered from the beginning of therapy **(BIII)**. Duration of therapy in treatment of candidemia 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. Treatment is recommended until 2 to 3 weeks after the last positive blood culture and signs and symptoms have resolved *[278]* **(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). Flucytosine has been used in combination with amphotericin B in some patients with severe invasive candidiasis, particularly in patients with CNS disease **(CIII)**, but has a narrow therapeutic index.

Fluconazole has been used as an alternative to amphotericin B for treatment of invasive disease in those who have not recently received azole therapy *[278]* **(AI)**. Treatment of invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease. Alternatively, an initial course of amphotericin B therapy can be administered and then carefully followed by completion of a course of fluconazole therapy **(BIII)**. Species identification is necessary when using fluconazole due to intrinsic drug resistance among certain *Candida* species (e.g., *C. krusei* and *C. glabrata*) **(EIII)**. Fluconazole given to children at 12 mg/kg/day provides exposure similar to standard 400 mg daily dosing in adults. Clearance in older adolescents can be similar to adults, so dosing above 600mg/day should be employed with caution *[289]*.

Antifungal agents in the echinocandin class including caspofungin, micafungin, and anidulafungin have been studied in adults with HIV infection, neutropenic children at risk of fungal infections, and children with documented candidiasis *[257, 290-295]*. Due to limited experience in children and no data in HIV-infected children, data are insufficient to recommend these drugs as first-line agents for invasive candidiasis in children **(CIII)**. The use of caspofungin in children with systemic candidiasis is limited. In a retrospective report in which caspofungin was administered to 20 children aged 0.1 to 16 years with invasive fungal infections (7 had invasive candidiasis) but without HIV infection, the drug was efficacious and well tolerated *[257]*. In a study of 10 neonates with persistent and progressive candidiasis and unknown HIV status, caspofungin was reported to be effective alternative therapy *[293]*. Micafungin has been studied in HIV-uninfected, neutropenic children at risk of invasive fungal infections. This drug demonstrates dose-proportional pharmacokinetics and an inverse relationship between age and clearance, suggesting a need for increased dosage in the young child *[294]*. A study of 19 Japanese HIV-uninfected children aged 0.6 to 15 years with confirmed invasive fungal infections, such as candidiasis, showed that plasma concentration of micafungin dosed at 3 mg/kg body weight was similar to that in adults given 150 mg per dose *[296]*. Micafungin was administered to premature infants who were receiving antifungal therapy for a suspected invasive fungal infection. Clearance of the drug in neonates was more than double the clearance in older children and adults *[295]*. Dosages of 10 – 15 mg/kg/day have been studied in premature neonates, resulting in area under the curve values consistent with an adult dose of 100 – 150 mg/day. One pharmacokinetic study of anidulafungin in HIV-uninfected neutropenic children aged 2 to 17 years showed drug concentrations at doses of 0.75 mg/kg per dose and 1.5 mg/kg per dose were similar to drug concentrations observed in adults with doses of 50 mg per dose and 100 mg per dose, respectively *[297]*.

There are limited data in adults on use of combination antifungal therapy for invasive candidal infections; combination amphotericin B and fluconazole resulted in more frequent clearance of *Candida* from the bloodstream but no difference in mortality *[298]*. There are insufficient data to support the routine use of combination therapy in children with invasive candidiasis *[248]* **(DIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

No adverse effects have been reported with the use of oral nystatin for treatment of oral candidiasis, but bitter taste might contribute to poor adherence.

The azole drugs have relatively low rates of toxicity but because of their ability to inhibit the CYP450-dependent hepatic enzymes (ketoconazole has the strongest inhibitory effect) they can have substantial interactions with other drugs undergoing hepatic metabolism. These interactions 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 such as PIs, should be carefully evaluated before initiation of therapy **(AIII)**.

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting (10% – 40% of patients). Skin rash and pruritus might be observed with all drugs; rare cases of Stevens-Johnson syndrome and alopecia 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 with itraconazole, including thrombocytopenia and leukopenia. Of the azoles, ketoconazole is associated with the highest frequency of side effects. Its use has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia, hemolytic anemia, and transaminitis. Dose-related, reversible visual changes (e.g., photophobia and blurry vision) have been reported in approximately 30% of patients receiving voriconazole *[299]*. Cardiac arrhythmias and renal abnormalities including nephritis and acute tubular necrosis also have been reported with voriconazole use.

Amphotericin B deoxycolate undergoes renal excretion as inactive drug. 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 minutes before the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Onset is usually within 1 to 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 rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur.

Lipid formulations of amphotericin B can cause acute, infusion-related reactions in approximately 20% of patients, including chest pain; dyspnea; 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 B infusion and administration of intravenous diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

Flucytosine has considerable toxicity: its effect on the bone marrow (e.g., anemia, leukopenia, thrombocytopenia), liver, GI tract, kidney, and skin warrants close monitoring of drug levels and dose adjustment to keep the level between 40 – 60 μg/mL. Therapeutic drug monitoring should be employed with this product, especially in patients with renal impairment. High levels can result in bone marrow suppression. The drug should be avoided in children with severe renal impairment **(EIII)**.

The echinocandins have an excellent safety profile. In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated and only 3 patients had adverse events that might have been related to the drug (hypokalemia in all 3 children, elevated bilirubin in 2, and decreased hemoglobin and elevated alanine aminotransferase in 1) *[255]*. In this study, children weighing <50 kg received doses ranging from 0.8 – 1.6 mg/kg body weight daily, and those weighing >50 kg received adult dosing. In the pharmacokinetic study of 39 children who received caspofungin at a dose of 50 mg/meter^2 body surface area/day, 5 (12.8%) patients experienced ≥1 drug-related clinical adverse event, including 1 patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. Two patients reported ≥1 drug-related laboratory adverse event, including 1 patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related adverse events in this study were considered serious or led to discontinuation of caspofungin *[255]*.

IRIS due to *Candida* infection has not been described in children; however, there may be evidence suggesting that candidiasis occurs with increased frequency in adults during the first 2 months after initiating HAART, with the exception of candidal eosophagitis *[300]*.

Management of Treatment Failure

Oropharyngeal and Esophageal Candidiasis

If initial therapy of OPC is with topical therapy, failure or relapse should be treated with oral fluconazole or itraconazole cyclodextrin oral solution *[283, 301]* **(AI)**.

Approximately 50% – 60% of patients with fluconazole-refractory OPC and 80% of patients with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution *[302, 303]* **(AII)**. Posaconazole is a second-generation orally bioavailable triazole that has been effective in HIV-infected adults with azole-refractory OPC and/or esophageal candidiasis *[304]*. However, experience in children is limited and appropriate pediatric dosage has not been defined; thus there are insufficient pediatric data to recommend its use in HIV-infected children *[305, 306]* **(CIII)**.

Amphotericin B oral suspension at a dose of 1 mL 4 times a day of a 100 mg/mL suspension has sometimes been effective among patients with OPC who do not respond to itraconazole solution; however, this product is not available in the United States *[303]* **(CIII)**. Low-dose intravenous amphotericin B (0.3 – 0.5 mg/kg/day) has been effective among patients with refractory OPC or esophageal candidiasis *[278, 303, 307, 308]* **(BII)**.

There is very limited experience with the use of echinocandins in the treatment of azole-refractory OPC or esophageal candidiasis in children (with or without HIV infection); however, given their excellent safety profile, the two echinocandins with the most pediatric data, caspofungin or voriconazole *[305]*, could be considered for treatment of azole-refractory esophageal candidiasis **(CIII)**.

Invasive Disease

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 pre-existing 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 *[309, 310]*, the drugs are considerably more expensive than conventional amphotericin B. Two lipid formulations are currently used, including amphotericin B lipid complex (ABELCET) and liposomal amphotericin B lipid complex (AmBisome). Experience with these preparations among pediatric patients is limited *[253, 311, 312]*.

For invasive candidiasis, amphotericin B lipid complex (ABELCET) is administered as 5 mg/kg body weight once daily given over 2 hours intravenously *[253, 311, 313]*. Amphotericin B liposome (AmBisome) is administered as 3 – 5 mg/kg body weight once daily over 1 to 2 hours intravenously. Duration of therapy is based on clinical response; most patients are treated for at least 2 to 4 weeks.

The role of the echinocandins in invasive candidiasis has not been well studied in HIV-infected children; however, neutropenic patients undergoing bone marrow transplantation have been successfully treated with this class of antifungals. These agents should be considered in the treatment of invasive candidiasis, but reserved as alternative, second-line therapy to currently available treatment modalities **(CIII)**.

Prevention of Recurrence

Secondary prophylaxis of recurrent OPC is generally not recommended because (1) treatment of recurrence is generally effective, (2) the potential exists for the development of resistance, (3) the issue of drug interactions, and (4) cost **(DIII)**. Immune reconstitution with HAART in children who are immunocompromised should be a priority **(AIII)**. However, if recurrences are severe, based on data in HIV-infected adults with advanced disease on HAART, suppressive therapy with systemic azoles, either oral fluconazole **(BI)** or itraconazole solution **(CI)**, can be considered *[314]*. Potential azole resistance should be considered when long-term prophylaxis with azoles is considered.

Based on data in HIV-infected adults, in children with fluconazole-refractory OPC or esophageal candidiasis who have responded to voriconazole or posaconazole therapy or echinocandins, continuing the effective drug as secondary prophylaxis may be considered because of high relapse rate until HAART produces immune reconstitution **(CI)**.

Discontinuing Secondary Prophylaxis

In situations where secondary prophylaxis is instituted, there are no data on which to base a recommendation regarding discontinuation, but it would be reasonable based on experience with HIV-infected adults with other OIs to discontinue secondary prophylaxis when the CD4 count or percentage has risen to CDC Immune Class 2 or 1.

Coccidioidomycosis

Epidemiology

Coccidioidomycosis is caused by the endemic dimorphic fungus, *Coccidioides* spp. Two species, *Coccidioides posadasii* and *C. immitis*, have been identified using molecular and biogeographical characteristics. *C. immitis* appears to be mainly confined to California, while *C. posadasii* is more widely distributed through the Southwestern United States, Northern Mexico, and Central and South America. Most reported infections in these endemic areas represent new infections. Clinical illnesses caused by each are indistinguishable. Infection results from the inhalation of spores produced by the fungal form in arid environments with hot summers preceded by rainy seasons *[315, 316]*. Reports of infections in nonendemic regions are usually a result of reactivation of a previous infection. Contaminated fomites, such as dusty clothing or agricultural products, have also been implicated as sources of infection *[317]*.

Pre-existing impairment of cellular immunity is a major risk factor for severe primary coccidioidomycosis or relapse of past infection. In HIV-infected adults, both localized pneumonia and disseminated infection are usually observed in individuals with CD4 counts <250 cells/mm^3 *[318, 319]*. The threshold for risk in HIV-infected children has not been determined. Systemic fungal infection has occurred when CD4 counts were ≤100 cells/mm^3 and with CD4% <15%; both indicative of severe immunosuppression *[1, 15]*. Although no cases of coccidioidomycosis opportunistic infection were reported in HIV-infected children from the Perinatal AIDS Collaborative Transmission Study (PACTS), the study sites were in locations that are not representative of the areas endemic for coccidioidomycosis *[4]*. While data are limited in children, in adults HAART appears to be responsible for a decline in the incidence of coccidioidomycosis *[320]*.

Clinical Manifestations

Immunocompromised individuals and previously healthy African Americans, Hispanics, and Filipinos with coccidioidomycosis are at an increased risk of dissemination, as well as pregnant women who acquire coccidioidal infection in the second or third trimester. Clinical manifestations of coccidioidomycosis in HIV-infected adults are well described. Among these are diffuse pulmonary disease; focal pneumonitis in the less immunocompromised patient; extrathoracic dissemination to meninges, lymph nodes, and/or liver; fever and weight loss syndrome with positive serologies; and the asymptomatic person with positive serologic tests *[319]*. If untreated, a coccidioidal antibody-seropositive, HIV-infected patient is at risk of developing serious disease. Bone and joint involvement is rarely observed in the HIV-infected patient *[320, 321]*.

Children with primary pulmonary infection may present with fever, malaise, and chest pain. Cough is variably present, and hemoptysis is rare. Persistent fever may be a sign of dissemination to extrathoracic sites. Children with meningitis may present with headaches, altered sensorium, vomiting, and focal neurological deficits. Fever is sometimes absent and meningismus occurs in only 50% of patients. Hydrocephalus is common and may occur early. Disseminated disease may also be accompanied by generalized lymphadenopathy, skin nodules or ulcers, peritonitis, and liver abnormalities.

Diagnosis

Since signs and symptoms of coccidioidomycosis are nonspecific, a high degree of suspicion is needed, particularly in nonendemic areas. Skin test negativity and seronegativity do not exclude the diagnosis in an HIV-infected patient.

In patients with meningitis, the CSF shows moderate hypoglycorrhachia, elevated protein concentration, and pleocytosis with a predominance of mononuclear cells. CSF eosinophilia has been reported.

The observation of distinctive spherules containing endospores in histopathologic tissue or clinical specimens is diagnostic. However, stains of CSF in patients with meningitis are usually negative. Pyogranulomatous inflammation with endosporulating spherules is seen readily with hematoxylin and eosin. Spherules can be observed using cytological staining methods, such as Papanicolau and Gomori methenamine silver nitrate stains. However, cytologic stains are less useful for the diagnosis of pulmonary coccidioidomycosis than they are for *Pneumocystis jirovecii*, and a negative cytologic stain on a clinical respiratory specimen does not rule out possible active pulmonary coccidioidomycosis *[321]*. Potassium hydroxide stains have a lower sensitivity and should not be used *[321]* **(DIII)**.

Growth of *Coccidioides* spp. is supported by many conventional laboratory media used for fungal isolation at 30°C – 37°C with growth occurring within 5 days *[321]*. However, blood cultures are positive in <15% of cases and <50% of CSF from children with meningitis will have a positive culture *[321]*. In contrast, cultures of respiratory specimens are frequently positive in cases of pulmonary coccidioidomycosis in adults.

Assays for coccidioidal antibody in serum or body fluids such as CSF provide valuable diagnostic and prognostic information. False-negative results may occur early in infection and in severely immunocompromised patients. Cross-reactivity may occur with other endemic mycoses. The presence of IgM-specific coccidioidal antibody suggests active or recent infection. The complement fixation (CF) assay detects IgG-specific antibody. CF titers become undetectable in several months if the infection resolves. The presence of standardized CF titers in excess of 1:16 directly correlates with the presence and severity of extrapulmonary dissemination. Serological tests may be falsely-negative in severely immunosuppressed, HIV-infected children. CF antibody is present in the CSF of 95% of patients with coccidioidal meningitis, although serial testing may be needed to demonstrate this. Titers decline during effective therapy.

Prevention Recommendations

Preventing Exposure

Although HIV-infected persons residing in or visiting regions in which coccidioidomycosis is endemic cannot completely avoid exposure to *Coccidioides* spp., exposure risk can be reduced by avoidance of activities that predispose to inhalation of spores. Such activities include disturbing contaminated soil, excavation of archaeological sites, and/or being outdoors during dust storms. If such activities are unavoidable, respiratory filtration devices should be considered.

Preventing First Episode of Disease

No prospective studies that examine the role of primary prophylaxis to prevent development of active coccidioidomycosis have been published. Although some experts would provide primary prophylaxis with an azole (e.g., fluconazole) to coccidioidal antibody-positive HIV-infected patients living in an endemic region, others experts would not *[321]*. Some experts would consider chemoprophylaxis for coccidioidal antibody-positive HIV-infected individuals considered at higher risk for development of active disease, including African Americans, those with unreconstituted cellular immunity with CD4 counts <250 cells/mm^3, and those with a history of thrush **(CII)** *[322]*. However, given the low incidence of coccidioidomycosis in pediatric HIV-infected patients, possibility of drug interactions, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of coccidioidial infections in children is not recommended.

Routine skin testing of HIV-infected patients with coccidioidin (spherulin) is not predictive of infection and should not be performed **(CIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

All patients with HIV infection who receive a diagnosis of clinically active coccidioidomycosis should be offered antifungal therapy. Treatment protocols for HIV-infected children are based on experience with adults in nonrandomized open-label studies. Physicians who infrequently treat children with coccidioidomycosis should consider seeking consultation from experts.

Because the critical factor in the control of coccidioidomycosis is cellular immune function, institution of effective antiretroviral therapy is also important in the treatment of disease and should be done contemporaneously with the initiation of antifungal therapy, if possible.

Diffuse pulmonary or disseminated infection should be treated with amphotericin B deoxycholate at a dose of 0.5 – 1.0 mg/kg/day **(AII)**. Amphotericin B treatment is continued until clinical improvement is observed. The dose and duration of amphotericin B depend on the severity of the symptoms, toxicity, and the rapidity of response. Total doses of amphotericin B deoxycholate in adults have ranged from 10 to 100 mg/kg. Thereafter, amphotericin B may be discontinued and treatment with fluconazole or itraconazole begun **(BIII)**. Some experts initiate therapy with amphotericin B combined with a triazole such as fluconazole in patients with disseminated severe disease and continue the triazole after amphotericin B is stopped *[321, 323]* **(BIII)**. The total duration of therapy should be ≥1 year *[321]*.

No clinical evidence supports greater efficacy of the lipid formulations of amphotericin B compared to deoxycholate. However, they are preferred when nephrotoxicity is of concern **(BI)**. A dose of 5 mg/kg/day is recommended for amphotericin B lipid complex and 3 – 5 mg/kg/day for liposomal amphotericin B.

For patients with mild disease (such as focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate given their safety, convenient oral dosing, and pharmacodynamic parameters **(BII)**. Thus, fluconazole (5 – 6 mg/kg/dose twice daily) or itraconazole (5 – 10 mg/kg/dose twice daily for 3 days followed by 2 – 5 mg/kg/dose twice daily) are alternatives to amphotericin B for children with mild, nonmeningitic disease **(BIII)**. In a randomized, double-blind trial in adults, fluconazole and itraconazole were equivalent in the treatment of nonmeningeal coccidioidomycosis. However, there was a trend toward itraconazole being superior for skeletal infections **(AI)** *[324]*.

Meningitis is distinct from other forms of coccidioidal infection, as an antifungal with CNS penetration is needed; thus, intravenous amphotericin B should not be used for coccidioidal meningitis. The relative safety and comparatively superior ability of fluconazole to penetrate the blood-brain barrier have made it the azole of choice for coccidioidal meningitis **(AII)**. Doses of fluconazole found to be effective in adults are 400 mg/day **(AII)**, but some experts begin therapy with 800 – 1,000 mg/day **(BIII)** *[323]*. Children usually receive dosages of 5 – 6 mg/kg/dose twice daily (800 mg/day maximum) **(AII)** *[9]*. Doses as high as 12 mg/kg/day have been used **(CII)** *[325]*. This dose is required to achieve serum concentrations equivalent to the adult dosing of 400 mg/day *[248]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

In addition to monitoring the patient for clinical improvement, monitoring coccidioidal CF IgG antibody titers is useful in assessing response to therapy. Titers should be obtained every 12 weeks **(AIII)**. A progressive decrease should be seen if therapy is succeeding, and a rise in titers suggests a recurrence of clinical disease. However, patients with serologic test results that were initially negative may have a delayed improvement in their serologic test results that does not correlate with clinical status *[321]*. This lag in response, occurring during the first 1 or 2 months of therapy, should not be construed as treatment failure.

Adverse effects of amphotericin B are primarily nephrotoxicity. Infusion-related fevers, chills, nausea, and vomiting can also occur, although they are less frequent in children than in adults. Lipid formulations of amphotericin B have lower rates of nephrotoxicity. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur (see discussion on Monitoring and Adverse Events in ***Candida* Infection**).

Triazoles may interact with CYP450-dependent hepatic enzymes, and the potential for drug interactions should be evaluated carefully before initiation of therapy **(AIII)**. Fluconazole and itraconazole appear to be safe in combination with antiretroviral therapy. Voriconazole should be avoided in patients receiving HIV PIs or NNRTIs *[319]*. The most frequent adverse effects of fluconazole are gastrointestinal, including nausea and vomiting. Skin rash and pruritis might be observed, and rare cases of Stevens-Johnson syndrome have been reported. Asymptomatic increases in transaminases can be observed in 1% – 13% of patients receiving azole drugs. In HIV-infected patients, fluconazole at high doses may cause adrenal insufficiency *[326]*.

Reports of coccidioidomycosis disease in response to IRIS have not been described in children.

Management of Treatment Failure

Limited clinical information is available for newer therapeutic agents. Posaconazole was shown to be effective in six patients with disease refractory to treatment with azoles and amphotericin B **(CII)** *[327]*. Voriconazole was effective in treating coccidioidal meningitis and nonmeningeal disseminated disease in patients who failed to respond to fluconazole and/or were intolerant of amphotericin B *[328, 329]*. Caspofungin alone was successful in treating disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and in individuals who have failed conventional therapy *[330, 331]*. Others have used caspofungin in combination with fluconazole *[332]*.

Adjunctive interferon-gamma was successfully used in a critically ill adult with respiratory failure who failed to respond to amphotericin B preparations and fluconazole *[333]*. However, there are no controlled clinical studies or data in children, so it is not recommended for use in HIV-infected children **(DIII)**.

Patients with coccidioidal meningitis who fail to respond to treatment with the azoles may improve with both systemic amphotericin B and direct instillation of amphotericin B into the intrathecal, ventricular, or intracisternal spaces with or without concomitant azole treatment **(CI)** *[324, 325]*. The basilar inflammation characteristic of coccidioidal meningitis commonly results in obstructive hydrocephalus necessitating the placement of a CSF shunt. The development of hydrocephalus in coccidioidal meningitis is not necessarily indicative of treatment failure.

Prevention of Recurrence

Relapse can occur in as many as 33% of patients with disseminated coccidioidomycosis even in the

absence of HIV infection, so lifelong antifungal suppression with either fluconazole or itraconazole is recommended for HIV-infected children with coccidioidomycosis **(AII)** *[321, 323, 334-336]*. In coccidioidal meningitis, excellent response rates to the azoles can be achieved, but cures are infrequent and relapse after cessation of therapy is common, occurring in as much as 80% of patients *[337]*. Thus, it is recommended that fluconazole therapy be continued indefinitely in patients with coccidioidal meningitis **(AII)**.

Discontinuing Secondary Prophylaxis

As with other disseminated fungal infections, continued suppressive therapy with fluconazole or itraconazole is recommended following completion of initial therapy. Patients with diffuse pulmonary disease, disseminated, or meningitic disease should remain on lifelong prophylaxis even if immune reconstitution is achieved with HAART because of high risk of relapse **(AIII)**. In HIV-infected adults with focal coccidioidal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 count >250 cells/mm^3 on HAART, some experts would discontinue secondary prophylaxis after 12 months of therapy with careful monitoring for recurrence with chest radiographs and coccidioidal serology **(CIII)**. However, the numbers of patients who have been evaluated are small and the safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied extensively. Therefore, for coccidioidomycosis among HIV-infected children, lifelong suppressive therapy is recommended after an acute episode of the disease, regardless of HAART therapy and immune reconstitution **(AIII)**.

Cryptococcosis

Epidemiology

Most cases of cryptococcosis in HIV-infected patients are caused by *Cryptococcus neoformans*; *C. gatti* (formerly *C. neoformans variety gatti*) infection occurs primarily in tropical and subtropical areas. Cryptococcal infections are much less frequent among HIV-infected children than among adults *[338-340]*. During the pre-HAART era, most cases of cryptococcosis in HIV-infected children (overall incidence, 1%) occurred in children aged 6 to 12 years and those with CD4 counts indicating severe immunosuppression *[340]*. Access to HAART has dramatically decreased the overall incidence of cryptococcal infection *[341, 342]*, and cryptococcosis in HIV-infected children on HAART remains exceedingly uncommon. Data from various PACTG studies in the pre- and post-HAART era indicate that the rate of invasive fungal infection, including cryptococcosis, has remained <0.1 per 100 patient-years *[1, 3]*. In the Perinatal AIDS Collaborative Transmission Study, no cases of cryptococcosis were identified in the HAART era *[4]*.

Clinical Manifestations

Cryptococcosis, not uncommonly, presents with subtle and nonspecific findings such as fever and headache. Early diagnosis requires consideration of this infection in a symptomatic patient with CD4 counts indicating severe immunosuppression. In both HIV-infected adults and children, meningoencephalitis is the most common initial manifestation of cryptococcosis. The disease typically evolves over days to weeks with fever and headache. Less frequent findings include nuchal rigidity, photophobia, and focal neurological signs, as were seen among 30 HIV-infected children with cryptococcosis reported from the United States *[340]*. In contrast to this indolent presentation, children in Zimbabwe presented with an acute form of neurologic cryptococcosis (69% with nuchal rigidity, 38% with seizure activity, and 23% with focal neurologic signs) *[343]*. CNS mass lesions (cryptococcomas) have not been reported to occur among HIV-infected children.

Disseminated cryptococcosis can be associated with cutaneous lesions, including small, translucent umbilicated papules (indistinguishable from molluscum contagiosum), nodules, ulcers, and infiltrated plaques resembling cellulitis. Diagnosis of pulmonary cryptococcosis without dissemination is unusual among children. Presenting findings include unexplained recurrent fever, cough with scant sputum, intrathoracic lymphadenopathy, and focal or diffuse pulmonary infiltrates. Alternatively the infection may be asymptomatic, with pulmonary nodules found on routine chest radiograph *[339]*.

Diagnosis

Detection of cryptococcal antigen in serum, CSF, or other body fluids is highly effective for rapid and accurate diagnosis of cryptococcal infection.

Microscopic examination of CSF on India ink-stained wet mounts should be performed for diagnosis of suspected CNS disease. CSF cell count, glucose, and protein can be virtually normal with CNS cryptococcosis, but the opening pressure is usually elevated. Cryptococcal antigen can be detected in CSF or serum by latex agglutination test (several manufacturers) from >90% of patients with cryptococcal meningitis. However, CSF antigen detection may be negative in culture-positive cryptococcal meningitis; high titers of antigen (prozone effect), low levels of antigen, and nonencapsulated strains contribute to this contradictory result *[344, 345]*.

Fungal cultures from CSF, sputum, and blood can identify the organism; the lysis-centrifugation method is the most sensitive for blood specimens. In some cases (e.g., patients with refractory or relapsed

disease), susceptibility testing of the *C. neoformans* isolate can be beneficial. Overall *in vitro* resistance to antifungal agents remains uncommon *[346]*.

Diffuse pulmonary disease can be diagnosed through bronchoalveolar lavage and direct examination of India ink-stained specimens, culture, and antigen detection. Focal pulmonary and skin lesions may require biopsy with culture and staining.

Prevention Recommendations

Preventing Exposure

There are no proven strategies for preventing exposure. *C. neoformans* infection is believed to be acquired via inhalation of aerosolized particles from the environment. Serologic studies of immunocompetent children in an urban setting indicate that most children are infected by *C. neoformans* after the second year of life *[347]*.

Preventing the First Episode of Disease

Because the incidence of cryptococcal disease is so low in HIV-infected children, routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended **(DIII)**. Additionally, given the low incidence of cryptococcosis in pediatric HIV-infected patients, lack of survival benefits in adult primary prevention studies, possibility of drug interaction, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of cryptococcal infections in children is not recommended.

A Cochrane Review of randomized controlled trials using antifungal interventions for the primary prevention of cryptococcal diseases indicates that fluconazole and itraconazole can reduce the frequency of cryptococcal disease among adult patients who have advanced HIV disease and severe immune suppression (CD4 count <50 cells/mm^3) *[348]*. However, neither of these interventions showed a clear effect on mortality.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Given the low incidence of cryptococcosis in HIV-infected children even in the pre-HAART era, management of this disease in this patient population has not been prospectively studied. Treatment recommendations reflect information extrapolated from many well-designed studies involving HIV-infected adults with cryptococcal meningitis.

Unlike immunocompentent hosts, in whom recovery from pulmonary infection without antifungal treatment can occur, immunocompromised hosts with cryptococcosis require treatment, since the condition is often fatal in the absence of treatment. Although antifungal treatment is effective, immune reconstitution of the host with the use of antiretroviral medications is crucial to the long-term outcome in terms of avoidance of episodes of recurrence and relapse. However, IRIS can be problematic in the short term, posing a diagnostic dilemma when it presents as clinical worsening in a host that was (or is being) treated appropriately for cryptococcal infection. Although limited data are available on how best to prevent and manage IRIS, because of the close proximity of diagnosis of OIs and initiation of HAART in patients who developed IRIS *[349, 350]*, some clinicians consider delaying initiation of HAART in treatment-naïve patients who have treatable OIs until after the acute phase of initial OI therapy has been

completed. Factors other than IRIS, such as tolerability of OI treatments and HAART and overlapping toxicities if both are started concurrently, are also reasons for delaying HAART initiation. There have been no clinical trials to assess optimal timing of initiation of HAART in patients with concurrent cryptococcosis. Overall *in vitro* resistance to antifungal agents used in the treatment of cryptococcosis remains uncommon *[346]*. Newer azoles (e.g., voriconazole, posaconazole, ravuconazole) are all very active *in vitro* against *C. neoformans [346]*, but there is limited published clinical experience of using them for cryptococcosis *[351, 352]*.

CNS Disease

The most common and well-studied presentation of cryptococcal infection in HIV-infected patients is CNS disease. In light of adult studies *[353-355]*, combination therapy with amphotericin B and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for pediatric patients **(AI)**. Cryptococci were cleared from CSF significantly more rapidly from adults with CNS disease who received initial therapy with amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) compared with those who received amphotericin B alone, amphotericin B plus fluconazole, or triple-antifungal therapy *[356, 357]*. In one adult study, liposomal amphotericin B (AmBisome) dosed at 4 mg/kg/day resulted in significantly earlier CSF culture conversion than did amphotericin B at 0.7 mg/kg/day *[358]*. Although cost differences associated with the formulation of amphotericin B influence the selection of one preparation over another, the liposomal preparation is preferred for patients with renal insufficiency **(AII)**. Monitoring for and managing raised intracranial pressure is crucial to the optimal management of CNS cryptococcosis (see below).

In patients who cannot tolerate flucytosine, amphotericin B (or its liposomal preparation) alone can be used for initial therapy **(BI)**. Fluconazole plus flucytosine is superior to fluconazole alone *[359, 360]* and provides an alternative to amphotericin B for acute therapy of invasive disease **(BII)**; however, few data are available regarding the use of this combination in children and it should only be used if amphotericin B-based therapy is not tolerated **(BIII)**. Although fluconazole monotherapy was an effective alternative to amphotericin B in adults with AIDS-associated cryptococcal meningitis *[361]*, concerns in this study about differences in early death, delayed CSF sterilization, and drug resistance *[362, 363]* make fluconazole monotherapy a less favorable option for initial therapy of CNS disease. Due to rapid development of resistance, flucytosine alone should never be used for treatment of cryptococcosis **(EII)**.

After a minimum of 2 weeks of induction therapy with evidence of clinical improvement and a negative CSF culture following repeat lumbar puncture, amphotericin B and flucytosine can be discontinued and consolidation therapy initiated with fluconazole **(AI)**. Consolidation therapy is continued for a minimum of 8 weeks *[364]*. Itraconazole is an alternative to fluconazole for the consolidation phase of CNS therapy and for secondary prophylaxis **(BI)**. Fluconazole is preferred because studies comparing the two agents demonstrate higher rates of CSF sterilization during consolidation therapy *[354]* and less frequent relapse *[364]* during maintenance therapy in fluconazole recipients.

Pulmonary and Extrapulmonary Cryptococcosis (CNS Disease Ruled Out)

There are no controlled clinical studies describing the outcome of non-CNS cryptococcosis in HIV-infected patients. CNS disease should be ruled out in all patients, after which the choice of antifungal medication and length of initial therapy can be decided in light of the clinical severity of illness. Patients with severe pulmonary disease or disseminated cryptococcosis should be treated with amphotericin B with or without the addition of flucytosine, as for CNS disease **(AIII)**. In general, combination therapy should be provided until symptoms resolve. Mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy **(AIII)**. Regardless of the antifungal agent selected for initial therapy, suppressive therapy with fluconazole or itraconazole should be continued long term.

Discontinuation of secondary prophylaxis can be considered in select cases (see note below on discontinuing secondary prophylaxis).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Monitoring for Raised Intracranial Pressure

Whenever a lumbar puncture is performed, opening pressure should be measured **(AII)**. Adult studies clearly show the role of increased intracranial pressure in mortality associated with CNS cryptococcosis *[354, 365]*. Health care providers should be vigilant regarding this condition. Its management includes repeated lumbar punctures. In rare cases, CSF shunting may need to be considered for patients who do not tolerate daily lumbar punctures or if signs and symptoms of cerebral edema are not being relieved with standard management. Corticosteroids and acetazolamide should not be used for reduction of intracranial pressure in cryptococcal meningitis **(DIII)**; acetazolamide was associated with severe acidosis, hypokalemia, and other adverse effects in a clinical trial among adults *[366]*.

Monitoring for Treatment Response

In addition to monitoring clinical response, mycologic response in patients with CNS cryptococcosis typically is assessed by a repeat lumbar puncture and CSF exam at 2 weeks, with continuation of induction therapy if the culture is positive until negative cultures are obtained.

Monitoring serial serum cryptococcal antigen titers is not useful for following treatment efficacy, because changes in serum cryptococcal antigen titers do not correlate well with outcome during treatment for acute meningitis or during suppressive therapy *[367, 368]*. Serial measurement of CSF cryptococcal antigen is more useful; in one study, an unchanged or increased titer of antigen in CSF was correlated with clinical and microbiological failure to respond to treatment and a rise in CSF antigen titer during suppressive therapy was associated with relapse of cryptococcal meningitis *[367]*. However, monitoring of CSF cryptococcal antigen levels requires repeated lumbar punctures and is not routinely recommended for monitoring response.

Monitoring for Adverse Events

Adverse effects of amphotericin B (Table 5) are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Close monitoring for drug toxicities is needed, especially when amphotericin B is used with flucytosine.

Flucytosine has the potential for marked toxicity, especially affecting the bone marrow (e.g., anemia, leukopenia, and thrombocytopenia), liver, GI tract, kidney, and skin. Patients receiving flucytosine should have flucytosine blood levels monitored to prevent bone marrow suppression and GI toxicity; peak serum levels, which occur 2 hours after an oral dose, should not exceed 75 μg/mL. Flucytosine should be avoided among children with severe renal impairment **(EIII)**.

Fluconazole and the other azoles have relatively low rates of toxicity, but their potential drug interactions can limit their use. Because of their ability to inhibit the CYP450-dependent hepatic enzymes, the potential for drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy **(AIII)**.

Immune Reconstitution Inflammatory Syndrome

Patients who develop cryptococcal IRIS are more likely to be severely immunocompromised with disseminated infection and to have initiated potent antiretroviral therapy soon after diagnosis of cryptococcal disease *[369]*; in antiretroviral-naïve patients newly diagnosed with cryptococcal meningitis,

it may be prudent to delay the initiation of potent antiretroviral therapy until the end of the first 2 weeks of induction therapy **(CIII)**.

IRIS related to cryptococcosis can present within weeks (e.g., meningitis) or months (e.g., lymphadenitis) after initiating HAART. Symptoms of meningitis are similar to those described at presentation. In one study, about 30% of all HIV-infected adults hospitalized for infection with *C. neoformans* who received HAART were readmitted with symptoms attributed to an inflammatory response *[349]*. Of the 18 patients with *C. neoformans*-related IRIS in the cited study, 17 had culture-negative meningitis, and most cases arose during the first 30 days after initiation of HAART. The most common presentation of late cryptococcal IRIS is lymphadenitis, particularly mediastinal lymphadenitis *[370]*.

The optimal management of cryptococcal IRIS has not been defined. Patients not already on antifungal therapy should have the antifungal therapy initiated and antiretroviral therapy should be continued **(AII)**. While many cases resolve spontaneously, anti-inflammatory therapy (e.g., short-course corticosteroids) has also been used by some experts in patients with severely symptomatic IRIS *[370, 371]* **(BIII)**.

Management of Treatment Failure

Treatment failure is defined as clinical deterioration despite appropriate therapy, including management of intracranial pressure; lack of improvement in signs and symptoms after 2 weeks of appropriate therapy; or relapse after an initial clinical response. Differentiating IRIS from treatment failure is important because treatment approaches and outcomes differ. Optimal management of patients with treatment failure is not known. If cultures are positive at the time of treatment failure, evaluation of antifungal susceptibilities may be considered, although fluconazole resistance with *C. neoformans* is rare in the United States (although more common in some international settings) *[362]*. Patients failing initial azole-based therapy should be switched to amphotericin B-based therapy *[362]*, ideally in combination with flucytosine **(BIII)**; the possibility of drug interactions resulting in subtherapeutic azole levels (e.g., concurrent rifampin use or other drugs metabolized by the liver) should be explored *[362]*. Use of liposomal amphotericin B should be considered, as one study suggests improved efficacy in CSF sterilization with liposomal preparations than with standard amphotericin B *[358]* **(AII)**. Some data from HIV-infected adults indicate higher doses (e.g., 400 – 800 mg/day) of fluconazole in combination with flucytosine can also be considered for salvage therapy *[355, 372]* **(BII)**. Clinical experience with new antifungal agents in the management of cryptococcosis is limited. A few patients with cryptococcal infections refractory or intolerant to standard antifungal therapy have been treated with posaconazole or voriconazole with variable success *[351, 352]*. Currently available echinocandins do not have clinical activity against cryptococcal infections and should not be used.

Prevention of Recurrence

Patients who have completed initial therapy for cryptococcosis should receive suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI)**. Fluconazole **(AI)** is superior and preferable to itraconazole **(BI)** for preventing relapse of cryptococcal disease *[364, 373, 374]*. Suppressive therapy typically is continued long term. Criteria for considering discontinuation of secondary prophylaxis are discussed below.

Discontinuing Secondary Prophylaxis

Until recently lifelong secondary prophylaxis was typically recommended. The safety of discontinuing secondary prophylaxis for cryptococcosis after immune reconstitution with HAART has not been studied in children, and decisions in this regard are to be made on a case-by-case basis. Adult patients at apparent low risk for recurrence of cryptococcosis have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained (≥6 months) increase in their CD4 counts to ≥200 cells/mm^3 after HAART *[375-377]*. In light of these observations

and inference from data regarding discontinuing secondary prophylaxis for other OIs during advanced HIV disease in HIV-infected adults, discontinuing chronic suppressive therapy for cryptococcosis (after being on it for ≥6 months) can be considered for asymptomatic pediatric patients aged ≥6 years, on HAART, and with sustained (≥6 months) increase in their CD4 counts to >200 cells/mm^3 **(BII)**. Suppressive therapy should be reinitiated if the CD4 count decreases to <200 cells/mm^3 **(AIII)**.

Histoplasmosis

Epidemiology

Histoplasmosis is caused by inhalation of microconidia produced by the mycelial form of *Histoplasma capsulatum*, an endemic dimorphic fungus that is widely distributed in the Ohio and Mississippi River valleys and in South America. Infections that occur in nonendemic regions often result from travel to these regions. The risk factors predisposing to infection are a CD4 count <150 cells/mm^3 and exposure to activities that disturb contaminated sites and result in aerosolization of spores. Since yeast forms of the fungus may remain viable within granulomas that were formed after successful treatment or spontaneous resolution of infection, late relapse may occur if cellular immune function wanes. Infection may occur during pregnancy and transplacental infection has rarely been reported *[378]*.

In the pre-HAART era, histoplasmosis was reported in 2% – 5% of HIV-infected adults in endemic regions; rates of 25% have been reported in some cities *[379]*. In a highly endemic region, histoplasmosis was the AIDS-defining illness in 25% of adults and 8% of children *[380]*. Progressive disseminated histoplasmosis (PDH) occurred in 5% of HIV-infected children in another highly endemic region *[M. Kleiman, unpublished observation]*. The overall incidence of histoplasmosis in children has not been systematically examined but appeared to be low even in the pre-HAART era *[1]*.

Few epidemiologic data concerning disseminated histoplasmosis in HIV-infected children and adolescents treated with HAART have been reported. In several combined PACTG cohorts, the incidence rate of all non-*Candida* invasive fungal infection was 0.10 (95% CI 0.05 – 0.20) infections per 100 patient-years in the pre-HAART era, and 0.08 (95% CI 0.03 – 0.17) infections per 100 patient-years in the HAART era *[1, 3]*. These data were contributed from centers that under represented the geographic regions of maximal histoplasmosis prevalence, so the statistical power to detect decreases in incidence rates associated with HAART may have been limited. However, it is likely that none of the rates of domestic endemic fungal infections (e.g., histoplasmosis, coccidioidomycosis, and blastomycosis) exceed these estimates in HIV-infected children and adolescents.

Clinical Manifestations

In children without HIV infection, acute pulmonary manifestations are common, but chronic pulmonary infection has not been described; because of greater airway pliability in children, airway obstruction due to mediastinal lymphadenopathy is more common in children *[381]*. While meningitis is common with progressive disseminated infection in infancy, subacute meningitis and parenchymal lesions characteristic of CNS disease in adults are unusual in children *[382]*. Isolated pulmonary granulomas resulting from past infections are common incidental findings in chest radiographs of asymptomatic individuals residing in endemic regions.

The most frequent clinical manifestation of histoplasmosis in HIV-infected children with AIDS is PDH; PDH is fatal if untreated. Prolonged fever and failure to thrive are uniform presenting complaints. There are few published reports of presenting signs and symptoms in children with PDH complicating AIDS *[380, 383-385]*. However, most are similar to those seen in PDH in otherwise normal infants and in infections in patients with other primary or acquired immunodeficiencies. These include splenomegaly, cough, respiratory distress, hepatomegaly, “septic” appearance, generalized lymphadenopathy, interstitial pneumonitis, cytopenia, coagulopathy, oropharyngeal/GI ulcerations, and/or erythematous nodular/ulcerative cutaneous lesions *[386-388]*.

Diagnosis

Culture, histopathologic, serological, antigen detection, and molecular diagnostic techniques have been developed to aid with diagnosis of histoplasmosis *[389, 390]*. Understanding their uses and limitations is essential to interpretation of results.

Histoplasmin skin tests are not currently available and were not useful for diagnosis of disseminated disease *[387, 388]*. Although isolation of the fungus using culture is diagnostic, it often requires invasive procedures, is insensitive, and growth may take 10 to 30 days. Growth of ***H. capsulatum*** is facilitated by lysis-centrifugation methodology and a DNA probe permits prompt identification of isolates *[391]*. Histopathologic demonstration of typical yeast forms in tissue specimens, bone marrow, or peripheral blood can be performed rapidly and, when positive, is highly suggestive of active infection. However, results are positive in only 12% – 43% of adults with PDH *[389]*. PCR and DNA probes have been developed for detection of ***H. capsulatum*** DNA in tissues *[392]* and body fluids *[393]*, but are neither sufficiently sensitive nor specific *[389, 390]*.

The interpretation of serologic testing using CF and immunodiffusion (ID) methods is problematic in immunocompromised hosts with PDH. CF titers of ≥1:32 to the yeast and/or mycelial antigens or the detection of H and/or M bands with the ID test are considered strongly suggestive of active or recent infection. However, only 41% of HIV-infected adults are seropositive when compared to 82% of those with PDH and no underlying immunocompromise *[394]*. Thus, seronegativity cannot be used to exclude active infection, especially PDH. Although a 4-fold increase in CF antibody is diagnostic of active infection, 2 to 4 weeks is needed to make this determination. CF antibody titers of CSF may be useful for the diagnosis of meningitis. In these instances, the assay should begin with undiluted specimens. Concurrent serum titers should be evaluated to exclude false positivity caused by blood contamination of the CSF *[382]*.

The development and refinement of an EIA that rapidly identifies and quantifies histoplasmal antigen in body fluids fills most of the gaps left by other diagnostic methods. EIA is especially suited for evaluating patients with large fungal burdens, a feature of infection in immunocompromised hosts. The EIA can detect antigen in serum, bronchoalveolar lavage, and CSF. The reported sensitivity of antigen detection is 91% – 92% in adults with PDH and 95% in adults with AIDS *[389, 390]*; sensitivity in children with underlying immunocompromise and in otherwise normal infants is 100% *[395]* and *[**M. Kleiman, unpublished observation**]*.

The current EIA has necessitated changes in recommendations for specimen submission and interpretation. In contrast to earlier, semi-quantitative assays, the third-generation EIA is standardized by extrapolating antigen concentrations from a calibration curve that is linear to a value of 39 ng/mL. However, urine antigen concentrations in serious infections frequently exceed this value. In these instances, serum specimens should be followed, since maximum serum concentrations are lower than those of urine and thus more likely to be in a range in which differences can be accurately measured. Following resolution of the antigenemia, urine concentrations can then be followed to monitor the effectiveness of treatment, and thereafter to identify relapse. Antigenuria is identified in 90% of patients who relapse *[381]*. The histoplasmal antigen assay has been shown to demonstrate cross-reactions with blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infections *[389, 390]*.

Antigen is detectable in 75% – 81% of immunocompetent hosts with acute, primary pulmonary infection. This occurs early in infection, reflecting the primary fungemia that is aborted by an effective cellular immune response. Thus, it is possible that antigenuria that occurs in a patient with HIV who retains normal cellular immunity may not presage development of disseminated infection.

Diagnosis of CNS infection is difficult, particularly if the patient has isolated meningitis without disseminated disease *[382]*. The highest sensitivity is achieved by testing CSF for histoplasmal antigen, antibody, and large volume culture. In adults, CSF culture is positive in only 20% – 60% of patients, CSF antigen is positive in 40% – 70%, and CSF antibody is positive in 70% – 90% *[389, 390]*. Meningitis frequently accompanies PDH of infancy *[386]*.

Prevention Recommendations

Preventing Exposure

Most infections occur without a recognized history of exposure to a high-risk site or activity. Therefore, complete avoidance of exposure in endemic regions is not possible. Sites and conditions commonly implicated in high-risk exposure and point source outbreaks include soil contaminated with bird or bat droppings, older urban and rural structures, decaying vegetation/trees, and caves. Dry and windy conditions, excavation, demolition, and gardening/agricultural activities predispose to aerosolization of spores. If avoidance of these activities is not feasible, reducing the release of spores by wetting soil, renovation sites, etc., and using protective respiratory devices *[396]* may reduce the likelihood of infection.

Preventing First Episode of Disease

Prophylaxis with itraconazole is recommended for HIV-infected adults whose CD4 count is <150 cells/mm^3 and who reside in highly endemic areas (i.e., incidence of histoplasmosis is >10 cases per 100 patient-years) and/or in instances in which there is high-risk occupational exposure. Prophylaxis had no effect on survival *[381]*. Given the low incidence of histoplasmosis in pediatric HIV-infected patients, possibility of drug interaction, potential antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of histoplasma infections in children is not recommended.

Discontinuing Primary Prophylaxis

Although studies have not been done to support the safety of discontinuing primary prophylaxis, the safety of discontinuing suppressive therapy (secondary prophylaxis) for HIV-infected adults with CD4 counts >150 cells/mm^3 has been demonstrated; treatment should be resumed if CD4 count falls below this threshold and the patient continues to reside in an area in which the threshold of >10 cases per 100 patient-years is exceeded *[381, 397]*. Prophylaxis is not recommended for HIV-infected children.

Treatment Recommendations

Treatment of Disease

PDH is fatal without treatment. Therapy with either amphotericin B deoxycholate or itraconazole *[398, 399]* is highly effective. The clinical response to amphotericin B is faster and it is preferred for the initial treatment of severe infections **(AI)**. Although amphotericin B may be used as monotherapy for an extended length of time, it is now more commonly used as induction therapy and is followed by long-term treatment with itraconazole. Itraconazole is the azole preferred for the treatment of histoplasmosis. Trials of therapy and the effectiveness of primary and secondary prophylaxis have been evaluated in HIV-infected adults. Recommendations for HIV-infected children are derived from these data and from anecdotal experience in children *[381]*. However, since there are important differences in the management of children with PDH, consultation with experts should be considered.

The dosage of liposomal amphotericin B for children is 3 – 5 mg/kg/day. Other less costly or better tolerated lipid formulations may be substituted for the liposomal product. Amphotericin B deoxycholate, at a dose of 1 mg/kg/day, is better tolerated by children than it is by adults, is effective, and may be used when cost of the lipid preparations is a consideration.

Itraconazole is usually well tolerated in children. Itraconazole has a long half-life and steady-state is not reached until 2 weeks. The interval needed to achieve desired serum concentrations can be shortened if the recommended dose is given three times daily for the initial 3 days of therapy ("loading dose"); the recommended dose given twice daily should be started thereafter. Itraconazole solution is preferred to the capsule formulation since it is better absorbed and serum concentrations are 30% higher than those achieved with the capsules. Since there is substantial intersubject variability in absorption of itraconazole, serum concentrations should be measured to ensure effective levels of drug, monitor changes in dosage, and assess compliance **(BIII)**. The MIC of *H. capsulatum* is 0.01 μg/mL and, though minimally effective serum concentrations have not been determined, a serum concentration of 1.0 μg/mL is recommended; dosage should be reduced if concentrations exceed 10 μg/mL *[381]*.

Fluconazole has been used successfully and is an alternative for patients with mild histoplasmosis who are intolerant of itraconazole or in whom desired serum levels cannot be attained. However, fluconazole is both less effective than itraconazole and has been associated with the development of drug resistance *[400]* **(CII)**. Ketoconazole is infrequently used due to its adverse reactions; it has been demonstrated to be effective in mild infections, excluding disseminated infection, and may be considered since it is much less costly than the other azoles.

Acute Primary Pulmonary Histoplasmosis

Exposure to a large fungal inoculum may result in fever, dyspnea, and diffuse pulmonary infiltrates. All patients, irrespective of immune status, should receive treatment with antifungal agents **(AIII)**. For severe or moderately severe symptoms, amphotericin B should be given for 1 to 2 weeks; amphotericin B deoxycholate is preferred as it is well tolerated in children **(AIII)** *[381]*. Following clinical improvement, patients with intact immunity should receive itraconazole, beginning with a loading dose (see above) for the first 3 days, then followed by the recommended dose given twice daily for at least12 weeks **(AIII)**; adults with CD4 counts of <150 cells/mm^3 and, by extrapolation, HIV-infected children with severe immunosuppression (e.g., CD4 <15% or <150 cells/mm^3 in children aged ≥6 years) should receive itraconazole for 12 months **(AIII)**. Urine antigen is usually elevated in these settings and should be monitored to gauge clinical response and, following treatment, identify relapse.

HIV-infected children, particularly those with functional cellular immunity, will occasionally present with fever associated with mild primary pulmonary infection, often associated with mildly to moderately elevated histoplasma urine antigen. While such illnesses may be self-limited by an effective cellular immune response, it may be prudent to treat with itraconazole for 12 weeks while following histoplasmal urine antigen concentrations to ensure that they decrease **(BIII)**.

Severe/Moderately Severe PDH

Based on data from HIV-infected adults, HIV-infected children with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous amphotericin B formulation for ≥2 weeks or until they clinically improve, followed by itraconazole for 12 months **(AI)**. In HIV-infected adults, moderately severe to severe PDH responds more favorably (88% vs 64%) and results in lower mortality (2% vs 13%) to liposomal amphotericin B than to the deoxycholate formulation **(AI)** *[381]*. Following a favorable clinical response, amphotericin B is discontinued and followed by "step-down" therapy with itraconazole for 12 months **(AII)**. A loading dose (see above) of itraconazole should be used for the initial 3 days. Should itraconazole not be well tolerated, a 4- to 6-week course of amphotericin B should be used and histoplasma urine antigen followed **(AIII)**.

Although therapeutic trials of amphotericin B deoxycholate used for the treatment of PDH in HIV-infected children have not been performed, this formulation is very effective for treating severe PDH in infants *[386, 401]*, including those with CNS infection *[386]*, and in children with other primary or

acquired immunodeficiency states. Amphotericin B deoxycholate is better tolerated by children than by adults, and it is less costly than other formulations. It may be used if cost or availability of lipid formulations precludes their use **(AIII)**.

Mild-to-Moderate PDH

Mild-to-moderate PDH in adults without signs of CNS infection has been shown to respond favorably in 80% – 100% of patients treated with itraconazole monotherapy for 12 months **(AII)** *[381, 398]*. This regimen is also recommended for HIV-infected children with mild-to-moderate PDH **(AII)**. A loading dose of itraconazole (see above) should be given at the onset of treatment and serum concentrations monitored.

CNS Infection

CNS infection that accompanies PDH is expected to respond to the regimen recommended for moderately severe to severe PDH. Isolated CNS infection is unusual in children. In adults, frequent failure and relapse are common and aggressive therapy is recommended. Liposomal amphotericin B is preferred for CNS disease in children and adults since it achieves higher concentrations in the brain **(AII)**; penetration into the CSF is poor with all formulations. The deoxycholate formulation is an alternative. Amphotericin should be given for 4 to 6 weeks. Thereafter, the child should receive a loading dose of itraconazole and continuation of itraconazole for 12 months **(AII)** and until CSF abnormalities, including histoplasmal antigen, have resolved. Antigen levels should be followed and dose adjusted to ensure optimal serum concentrations.

Asymptomatic Histoplasma Granuloma

In asymptomatic HIV-infected children who have intact cellular immunity and have resided in an endemic area, the presence of a typical granuloma in a chest radiograph should prompt evaluation of both histoplasmal urine antigen and CF and ID antibody. If any of these tests are positive, treatment with itraconazole for 12 weeks is prudent **(BIII)**. If negative, therapy need not be used and clinical follow-up is recommended. In either instance, histoplasmal urine antigen testing should be considered if unexplained fever or other systemic symptoms occur.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for a year thereafter to identify relapse **(AIII)** *[402]*. Following a recommended course of therapy and, in the absence of symptoms, low-level, stable antigenuria may not constitute a basis for prolonging the recommended course of therapy. Serum levels of itraconazole should be monitored in patients receiving treatment.

Adverse effects of amphotericin B are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, although they are less frequent in children than in adults. Renal dysfunction and electrolyte imbalances are its primary toxicities; these parameters should be monitored during therapy

Itraconazole, as other azoles, has relatively low rates of toxicity. GI upset is seen occasionally and its principal toxicity is hepatic. The azole drugs inhibit CYP450-dependent hepatic enzymes so that drug interactions, particularly with antiretroviral drugs, should be carefully evaluated before initiation of therapy.

IRIS caused by an inflammatory response to histoplasmosis unmasked by HAART-induced improvement in cellular immunity is unusual and symptoms are often mild *[403]*. In the event of its occurrence, antiretroviral therapy should be continued along with antifungal therapy.

Management of Treatment Failure

Both voriconazole and posaconazole have been used successfully in a small number of refractory cases in adults *[381]*. Since little experience has been reported using the newer azoles and there are only limited data on use of these agents in children, expert consultation is recommended for cases refractory to first-line agents.

Prevention of Recurrence

Children responding well after completion of initial amphotericin B treatment should be continued on oral itraconazole maintenance therapy for at least 1 year **(AII)**. Longer term suppressive therapy with itraconazole may be required in HIV-infected children who are severely immunosuppressed (i.e., CD4 <15% or <150 cells/mm^3 in children aged ≥6 years) and patients who experience relapse despite receipt of appropriate therapy **(AII)** *[381, 397]*. Fluconazole is less effective than itraconazole **(CII)** and there is only limited experience in children with voriconazole.

Discontinuing Secondary Prophylaxis

Though not examined in children, based on data from a clinical trial evaluating discontinuation of treatment in adults with immune restoration on HAART, discontinuation of itraconazole is recommended in adults if itraconazole has been received for ≥1 year, blood cultures are negative, histoplasmal serum antigen is <2 ng/mL, CD4 counts are >150 cells/mm^3, and the patient is compliant with HAART therapy *[397]* **(AI)**. Extrapolating these recommendations to HIV-infected children on HAART with immune restoration (i.e., CD4 >15% or CD4 >150 cells/mm^3 in children aged ≥6 years) seems reasonable **(CIII)**. Treatment should be resumed if these parameters are not met. Chronic suppressive therapy is recommended for patients who relapse despite appropriate treatment.

Pneumocystis Pneumonia

Epidemiology

Pneumocystis species are found worldwide in the lungs of humans and lower mammals. The organisms are host specific and cross-infection between humans and other animals does not occur. *Pneumocystis* spp. from all sources are morphologically, tinctorially, and biologically similar, but host-specific differences have been demonstrated by surface antigens and by gene sequencing. Since the original designation of *Pneumocystis carinii* a century ago, several changes in terminology have been suggested. The most recent proposal to change *P. carinii* to *Pneumocystis jirovecii* for isolates from human lungs has gained some popularity, but remains controversial.

Pneumocystis has been designated a fungus based on DNA analysis but has several biologic features of protozoa. It is one of the most frequent causes of infection in humans. By 2 to 4 years of age more than 80% of children in most countries have acquired antibodies to *Pneumocystis [404-406]*. Immunocompetent infants with the infection are either asymptomatic or may have mild respiratory symptoms. *Pneumocystis* pneumonitis (PCP) occurs almost exclusively in the immunocompromised host.

PCP remains a common AIDS-indicator disease among HIV-infected children. The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at age 3 to 6 months *[407-409]*. Data from the CDC Pediatric Spectrum of Disease Project (1994 – 2001) indicate a decline in PCP infection rates (cases per 1,000 HIV-infected children) from 25 in 1994 to 18 in 1996 and to 6 in 2001 *[1, 410]*. Similarly, analyses of data from the Perinatal AIDS Collaborative Transmission Study (PACTS) revealed a 95% decline in PCP (cases per 100 patient-years) from 5.8 (pre-HAART era) to 0.3 (HAART era) *[4]*. Finally, the incidence rate of PCP (cases per 100 person-years) was 1.3 from the pre-HAART era (1981 – 1988) and <0.5 during the HAART era (2001 – 2004) *[3]*. This decline was likely due to the implementation of interventions to prevent mother-to-child transmission of HIV, the introduction of HAART in HIV-infected children in 1995, and chemoprophylaxis for PCP.

PCP is a major cause of death among HIV-infected infants and children in Africa. Autopsies revealed PCP in 16% of children dying with HIV/AIDS from 1992 to 1993 *[411]*, in 29% of those dying from 1997 to 2000 *[412]*, and in 44% of those dying from 2000 to 2001 *[413]*.

The mode of transmission of *Pneumocystis* among HIV-infected infants, children, and adults is not firmly established, but human-to-human transmission is likely to occur by the airborne route. Animal studies show *Pneumocystis* to be transmitted by air from infected to susceptible rats *[414, 415]*. Human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases in recent studies *[416-418]*. Intrauterine transmission is considered rare. However, in one report, one of eight infants born to women with AIDS and PCP during pregnancy had evidence of *Pneumocystis* infection *[419]*.

The single most important factor in susceptibility of HIV-infected patients of all ages to PCP is the status of cell-mediated immunity of the host. Severe compromise, reflected by a marked decrease in CD4 count and percentage, is the hallmark of high risk for PCP and is discussed further under the prevention section.

Clinical Manifestations

Prominent clinical features of PCP among HIV-infected children are fever, tachypnea, dyspnea, and cough. The severity of these signs and symptoms may vary from child to child. Onset can be abrupt or insidious with nonspecific symptoms (e.g., mild cough, dyspnea, poor feeding, diarrhea, and weight loss). Some patients may not be febrile, but almost all patients will have tachypnea by the time pneumonitis is

observed on chest radiograph. Physical examination may, or may not, show bilateral basilar rales with evidence of respiratory distress and hypoxia.

In HIV-infected children with pneumonia, 4 clinical variables independently associated with PCP are: age <6 months, respiratory rate >59 breaths per minute, arterial percentage hemoglobin saturation (SaO_2) ≤92%, and the absence of vomiting *[420]*. A high plasma HIV RNA concentration is a strong predictor of PCP and other OIs *[421]*.

Extrapulmonary *Pneumocystis* organisms are found in <2.5% of HIV-infected adults and children *[422, 423]*. This can occur without concurrent PCP and can be located at multiple noncontiguous sites. Involved sites have included ear, eye, thyroid, spleen, GI tract, peritoneum, stomach, duodenum, small intestine, transverse colon, liver, and pancreas. Less frequently involved sites include adrenal glands, muscle, bone marrow, heart, kidney, ureter, lymph nodes, meninges, and cerebral cortex.

Diagnosis

The majority of children with PCP have substantial hypoxia with low arterial oxygen pressure and an alveolar-arterial oxygen gradient of >30 mmHg. The CD4 count is often <200 cells/mm^3 and the CD4 percentage <15% in children aged >5 years. Lactic dehydrogenase is often increased but this is not specific for PCP. Serum albumin may be depressed. Chest radiographs most commonly indicate bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance, but they also may be normal or have only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally before reaching the apical portions of the lung. Rarely, lobar, cavitary, nodular, or miliary lesions; pneumothorax; or pneumomediastinum are observed.

A definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids in the presence of pneumonitis. Diagnostic procedures are the same as used for adults with suspected PCP (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*, but some procedures may be more difficult to perform in children. Several procedures for the collection and staining of specimens are available.

Induced sputum analysis, where the patient produces sputum after inhalation of nebulized 3% hypertonic saline, may be difficult among children aged <2 years because of small airways and poor ability to produce sputum. Complications from the procedure include nausea, vomiting, and bronchospasm. Sensitivity of sputum analysis in adults ranges from 25% to 90%. The negative predictive value is only 48%. Following a negative induced sputum sample, a bronchoalveolar lavage (BAL) for definitive diagnosis may be necessary.

Nasogastric aspirates, if positive, are of diagnostic value. Gastric aspirates obtained on 3 consecutive mornings from HIV-infected children with respiratory illnesses were found to have *Pneumocystis* organisms in 48.6% of the cases *[424]*. Other studies have shown the organism is not found in gastric contents without PCP *[425]*.

Bronchoscopy with BAL is the diagnostic procedure of choice for most infants and children. Sensitivity ranges from 55% to 97% and may be positive for ≥72 hours after PCP treatment has been initiated; treatment should not be delayed while awaiting results. Complications include hemoptysis, pneumothorax, a transient increase in hypoxemia, a transient increase in pulmonary infiltrates at the lavage site, and post-bronchoscopy fever.

Fiberoptic bronchoscopy with transbronchial biopsy is recommended only when BAL is negative or nondiagnostic despite the child having a clinical picture consistent with PCP. Sensitivity is 87% – 95%

and cysts can be identified up to 10 days after initiation of treatment (up to 4 to 6 weeks in certain patients). Complications include pneumothorax and hemorrhage; this procedure is contraindicated in children with thrombocytopenia.

Open-lung biopsy is the most sensitive and specific diagnostic technique, but because it requires thoracotomy and often chest tube drainage, it is not recommended routinely. It has the advantage of revealing the type and extent of disease as well as the organism. Histopathology shows alveoli filled with eosinophilic, acellular, proteinaceous material that contains cysts and trophozoites but few inflammatory cells. Complications include pneumothorax, pneumomediastinum, and hemorrhage.

Three types of stains can be used to identify *Pneumocystis* organisms in specimens. Gomori's methenamine-silver method stains the cyst wall brown or black. Toluidine blue stains the cyst wall blue or lavender. Both methods stain fungal elements. Giemsa, Diff-Quick®, and Wright's stains depict the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus but, unlike other stains, these do not stain the cyst wall. Monoclonal immunofluorescent antibodies (Merifluor®, Meridian Bioscience, Inc., Cincinnati, OH) that stain the cyst wall also can be used for diagnosis and have enhanced specificity compared to the other methods. A cyst wall, trophozoite, and immunofluorescent antibody stain is recommended for each specimen studied.

PCR assays to amplify the human *Pneumocystis* MSG gene, mitochondrial large subunit (mtlsu) rRNA, the dihydropteroate synthase gene, and the internal transcribed spacer region genes have been developed for diagnostic evaluation. These tests are usually more sensitive but less specific when compared to microscopic methods and are not standardized or available in most centers *[426, 427]*. Noteworthy is the finding that *Pneumocystis*-specific DNA is found in 18% of BAL samples from patients without clinical PCP, HIV, and other infections *[428]*.

Coinfection with other organisms (e.g., CMV or pneumococcus) has been reported in HIV-infected children *[409, 429, 430]*. Children with dual infections may have more severe disease. Although the presence of CMV in lung secretions of children with PCP indicates colonization, it usually does not require therapy. The presence of *Pneumocystis* is always an indication for treatment.

Prevention Recommendations

Preventing Exposure

The need for contagious isolation of hospitalized PCP cases has been neither demonstrated nor discounted. Clearly, there is no need to isolate PCP cases from individuals with normal immune responses and from immunocompromised high-risk patients who are receiving PCP prophylaxis. Under unusual circumstances where prophylaxis cannot be given, room isolation of either the infected or the susceptible patient may be warranted **(CIII)**.

Preventing First Episode of Disease

Chemoprophylaxis is highly effective in the prevention of PCP. Criteria for its use are based on the patient's age and CD4 count or percentage **(AII)**. Prophylaxis is recommended for all HIV-infected children aged ≥6 years with CD4 counts <200 cells/mm^3 or CD4 <15%, for children aged 1 to 5 years with CD4 counts of <500 cells/mm^3 or CD4 <15%, and for all HIV-infected infants aged <12 months regardless of CD4 count and percentage *[431]*.

Infants born of HIV-infected mothers should be considered for prophylaxis beginning at 4 to 6 weeks of age. HIV-infected infants should be given prophylaxis until 1 year of age, at which time reassessment is made based on the age-specific CD4 count or percentage thresholds mentioned above **(AII)**. Infants with

indeterminate HIV infection status should receive prophylaxis until they are determined to be HIV uninfected or presumptively uninfected with HIV. Prophylaxis is not recommended for infants who meet criteria for HIV-uninfected and presumptively uninfected with HIV status. In nonbreastfeeding infants with no positive HIV virologic test results, presumptive exclusion of HIV infection can be based on two negative virologic test results, one obtained at ≥2 weeks and one obtained at ≥4 weeks of age; one negative virologic test result obtained at ≥8 weeks of age; or one negative HIV antibody test result obtained at ≥6 months of age. Definitive exclusion of HIV infection is based on two negative virologic test results, one obtained at ≥1 month of age and one obtained at ≥4 months of age, or two negative HIV antibody test results from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, the child should have no other laboratory (e.g., no positive virologic test results) or clinical (e.g., no AIDS-defining conditions) evidence of HIV infection.

Four drug regimens have been found effective and relatively safe for the prevention of PCP in high-risk HIV-infected children and adults:

TMP-SMX (cotrimoxazole) is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(AI)**. Trimethoprim alone has little, if any, anti-*Pneumocystis* activity but it enhances the activity of the sulfonamide. The prophylactic dosage is 150 mg/meter^2 body surface area/day TMP and 750 mg/meter^2 body surface area/day SMX (approximately 5.0 mg/kg/day TMP and 25 mg/kg/day SMX) given orally in equally divided doses twice a day 3 consecutive days per week *[432]*. The total daily dose should not exceed 320 mg TMP and 1,600 mg SMX. For patients with impaired renal function, a reduced dose may be necessary.

Alternatively, TMP-SMX may be administered daily 7 days a week *[433]* **(AI)**. Note that TMP-SMX is also effective in the prevention of toxoplasmosis *[434]* and some bacterial infections (*Salmonella*, *Haemophilus*, *Staphylococcus*, and others) *[433, 435-437]*.

Dihydropteroate synthase (DHPS) gene mutations in *Pneumocystis* from humans have been observed with TMP-SMX and dapsone prophylaxis, suggestive of possible drug resistance, but studies for clinical correlates have not provided conclusive results *[426]*. More apparent is the association of prolonged TMP-SMX prophylaxis for PCP with the emergence of selective pressure resistance of clinically important bacterial species to TMP-SMX, a point to be considered in the management of bacterial infections occurring in patients receiving prophylaxis *[438, 439]*.

Other effective and safe prophylaxis regimens are available for those who are unable to take TMP-SMX. A second choice would be either atovaquone or dapsone *[440]* **(BI)**. Atovaquone is effective and safe but expensive. Dapsone is effective and cheap but associated with more serious adverse effects than atovaquone.

Atovaquone is administered with a meal as an oral yellow suspension in a single dose of 30 mg/kg/day for patients 1 to 3 months and >24 months of age, and 45 mg/kg/day for infants aged 4 to 24 months *[441]*. Unlike TMP-SMX, atovaquone has no antibacterial activity, but is effective against *Toxoplasma gondii*. Azithromycin in a single dose of 5.0 mg/kg/day has been used to supplement atovaquone for greater broad-spectrum prophylaxis. The randomized, double-blind, placebo-controlled study PACTG 254 compared TMP-SMX and atovaquone plus azithromycin for a period of 3 years (median) in 366 HIV-infected children qualifying for PCP prophylaxis *[95]*. Results showed atovaquone-azithromycin to be as effective as TMP-SMX for the prevention of serious bacterial infections as well as PCP.
Dapsone may be given on a daily or weekly schedule as 2.0 mg/kg/day (maximum total dose of 100 mg/day) or 4.0 mg/kg/week (maximum total dose of 200 mg/week) orally. Approximately two-thirds of patients intolerant to TMP-SMX can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or aerosolized pentamidine but slightly less effective than TMP-SMX *[440, 441]*.

Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and are old enough to use nebulization with a Respirgard II® nebulizer (Marquest, Englewood, CO) **(BI)**. The dosage for all ages is 300 mg once a month *[436]*. Adverse reactions among HIV-infected children include cough, sneezing, and bronchospasm *[442]*.

Pyrimethamine-sulfadoxine (Fansidar®) is also recognized as an effective prophylaxis regimen in adults **(CIII)**. Although this drug was found to be effective in the prevention of PCP in Iranian orphanages in the 1960s, it has not been evaluated adequately among HIV-infected pediatric patients.

The use of intravenous pentamidine is not recommended for prophylaxis **(EIII)** *[443]*.

Discontinuing Primary Prophylaxis

Studies of HIV-infected adults and children following immune reconstitution after receipt of HAART demonstrate acceptable low risks for PCP after discontinuation of prophylaxis *[46, 444-448]*. Data from the PACTG 1008 study evaluated 235 HIV-infected children and adolescents on antiretroviral therapy who received PCP prophylaxis ≥6 months and achieved CD4 percentages of ≥20% for patients aged >6 years and ≥25% for patients aged 2 to 6 years, after which the prophylaxis was stopped *[46]*. During the median follow-up period of 2.5 years (547 person-years), no cases of PCP occurred; 9.4% of patients enrolled required reinstitution of PCP prophylaxis during the observation period. These data along with those from adult studies support the expectation for very low risk of PCP after discontinuation of prophylaxis for children who have achieved immune reconstitution.

It is recommended that consideration be given to discontinuation of PCP prophylaxis for HIV-infected children when, after receiving HAART for ≥6 months, CD4 percentage is ≥15% or CD4 count is ≥200 cells/mm^3 for patients aged >6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients aged 1 to 5 years **(BII)** for >3 consecutive months. Subsequently, the CD4 percentage and count should be re-evaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached **(BIII)**. PCP prophylaxis is not to be discontinued in HIV-infected infants aged <1 year.

Treatment Recommendations

Treatment of Disease

TMP-SMX is the recommended treatment for PCP **(AI)**. The dose for HIV-infected children aged >2 months is 15 – 20 mg/kg/day of the TMP component and 75 – 100 mg/kg/day of the SMX component administered intravenously in three to four divided doses, with the dose infused over 1 hour for 21 days **(AI)**. As the acute pneumonitis subsides, 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 three to four divided doses to complete a 21-day course **(AII)**. Effective therapeutic serum concentrations of 5 – 10 μg/mL TMP can be achieved with the recommended dose given orally in HIV-infected children *[449]*.

Intravenous pentamidine isethionate once daily is recommended for patients intolerant of TMP-SMX or who demonstrate clinical treatment failure after 5 to 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 to 10 days of intravenous therapy with pentamidine, an oral regimen (e.g., atovaquone or trimethoprim/dapsone) might be considered to complete a 21-day course **(BIII)**.

Atovaquone is an alternative for treatment of mild to moderately severe PCP in adults *[95]* **(BI)**. Therapeutic data are limited for children but the dosage of 30 – 40 mg/kg/day in two divided doses given orally is established for individuals <3 months and ≥24 months of age. Children aged 3 to 24 months require a higher dosage of 45 mg/kg/day *[441]* **(AII)**. The dose for adolescents and adults is 750 mg twice daily. Food increases the bioavailability of atovaquone to ≥3-fold more than that achieved with the fasting state. Atovaquone concentration is increased with coadministration of fluconazole and prednisone and decreased by coadministration with acyclovir, opiates, cephalosporins, rifampin, and benzodiazepines.

Dapsone/trimethoprim is effective in the treatment of mild-to-moderate PCP among adults *[450]* **(BI)**; data on toxicity and efficacy among children are limited**.** The dose of dapsone for adolescents and adults is 100 mg (total dose) orally once daily and trimethoprim 15 mg/kg/day divided into three daily doses 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 *[451]* **(AII)**. The pediatric dose of TMP is 15 mg/kg/day divided into three daily doses. Dapsone is less effective than the combination *[452]*.

Clindamycin/primaquine has been used for treatment of mild-to-moderate PCP among adults **(BI)**; data for children are not available. Primaquine is contraindicated for patients with glucose-6-dehydrogenase deficiency due to 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 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 infection is 10 mg/kg/dose every 6 hours, and the pediatric dose of primaquine equivalent to an adult dose of 20 mg base (when used for malaria) is 0.3 mg/kg/day of the base.

On the basis of studies in adults, a short course of corticosteroids is recommended in some cases of PCP of moderate or severe intensity, starting within 72 hours of diagnosis **(AI)**. Pediatric studies have indicated a reduction in acute respiratory failure, a decrease in the need for ventilation, and a decrease in mortality with early use of corticosteroids in HIV-infected children with PCP *[453-455]*. Indications for corticosteroid treatment include a PaO_2 value of <70 mmHg or an alveolar-arterial gradient of >35 mmHg. Doses for children vary between studies. A commonly used scheme is prednisone on Days 1 to 5, 1 mg/kg/dose twice daily; Days 6 to 10, 0.5 mg/kg/dose twice daily; and Days 11 to 21, 0.5 mg/kg once daily. Alternative regimens include: (1) adult dosage prednisone on Days 1 to 5, 40 mg twice daily; Days 6 to 10, 40 mg once daily; Days 11 to 21, 20 mg once daily; and (2) methylprednisolone (intravenous) on Days 1 to 7, 1 mg/kg/dose every 6 hours; Days 8 to 9, 1 mg/kg/dose twice daily; Days 10 to 11, 0.5 mg/kg/dose twice daily; Days 12 to 16, 1 mg/kg once daily.

Some case reports 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) *[456-458]* **(CIII)**. Alterations in surfactant function and composition have been demonstrated in HIV-infected patients with PCP *[459]*. No therapeutic schemes have been established.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Clinical parameters to monitor the status of disease include temperature, respiratory rate, arterial oxygen saturation, and chest radiograph *[460]*. Clinical improvement can be expected at around a mean of 4.5 ± 2.5 days and radiographic improvement at around 7.7 ± 4.5 days *[460]*.

IRIS has been less frequently associated with *Pneumocystis* infection (2% of 44 adults with IRIS) than several other OIs in HIV-infected adults and children *[461]*. Whether this low rate is related to PCP prophylaxis is not known.

In children, adverse reactions to TMP-SMX include rash (mild maculopapular in most cases but rarely erythema multiforme and Stevens-Johnson syndrome), hematologic abnormalities (e.g., neutropenia, thrombocytopenia, megaloblastic or aplastic anemia), GI complaints (usually mild), hepatitis, and renal disorders (e.g., interstitial nephritis) *[462, 463]*. Data from a PACTG study of HIV-infected children at high-risk for PCP receiving TMP-SMX for a median of 3 years showed 28% had a rash, 9.3% neutropenia, 8.8% thrombocytopenia, and 2.2% anemia *[95]*. None were fatal or nonreversible reactions. Some very mild reactions will resolve while the drug is continued. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. Unless the reaction has been life-threatening, TMP-SMX prophylaxis can be resumed, preferably by beginning with low desensitizing daily doses and gradually increasing to full doses *[464, 465]* **(BII)**. In adults, 75% of patients affected are able to tolerate rechallenge with TMP-SMX *[465]*. 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 *[445]*. If an urticarial rash or Stevens-Johnson syndrome occurs, TMP-SMX should be discontinued and not readministered **(EIII)**.

The most common adverse drug reaction to pentamidine isethionate 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 to 7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus have also been reported. A metallic or bitter taste may be experienced. Serious adverse reactions to pentamidine have been reported in approximately 17% of children receiving the drug *[466]*. Care should be taken to avoid administering this drug with other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) and with agents associated with pancreatitis (e.g., didanosine).

With dapsone and trimethoprim, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemaglobinemia, anemia, and thrombocytopenia *[450, 452]*. Dapsone is the problematic component of the combination and accounts for most of the adverse reactions *[441]*.

Skin rashes (10% – 15%), nausea, and diarrhea may occur with atovaquone administration. Transient increase in liver enzymes may occur. No serious toxicity or fatality has been demonstrated from the use of atovaquone in adults or children.

Adverse reactions to clindamycin/primaquine include skin rash, nausea, and diarrhea.

Management of Treatment Failure

There can be an initial early and reversible deterioration in the first 3 to 5 days of therapy, likely due to an inflammatory reaction to antibiotic-induced killing of the organism in the lungs, so an adequate trial of therapy is needed before switching drugs for lack of clinical improvement. Clinical failure is defined by the lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Other concomitant infections need to be excluded as a cause of clinical failure. With evidence of treatment failure after the use of TMP-SMX, drugs can be changed. If tolerated, pentamidine isethionate is the drug of next choice **(BII)**. No evidence exists for synergistic or additive therapeutic effects; therefore, because of potential increased toxicity their combination is not recommended.

Prevention of Recurrence

It is important to note that none of the drugs administered for the treatment and prevention of PCP completely eradicates *Pneumocystis* and that prophylaxis is effective only while the selected drug is administered. Patients who have experienced an episode of PCP should have prophylaxis administered continuous with completion of treatment **(AI)**.

Discontinuing Secondary Prophylaxis

In most patients secondary prophylaxis may be discontinued using the same criteria as for the discontinuation of primary prophylaxis. Thus, consideration may be given to discontinuation of PCP prophylaxis for HIV-infected children when, after receiving HAART for ≥6 months, CD4 percentage is ≥15% or CD4 count is ≥200 cells/mm^3 for patients aged >6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients aged 1 to 5 years **(BII)** for >3 consecutive months. Subsequently, the CD4 percentage and CD4 count should be re-evaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached or if PCP recurs **(BIII)**. PCP prophylaxis is not to be discontinued in HIV-infected infants <1 year. Individuals who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite normal or high CD4 counts or percentages *[467]* **(BII)**.

PARASITIC INFECTIONS: Cryptosporidiosis/Microsporidiosis

Epidemiology

Cryptosporidium species are protozoal parasites that mainly cause enteric illness (e.g., chronic diarrhea) in humans and animals; the parasites have worldwide distribution. The three most common species infecting humans are *C. hominis*, *C. parvus*, and *C. meleagridis*. In addition, infections with *C. canis*, *C. felis*, *C. muris*, and *Cryptosporidium* pig genotype have been reported in immunocompromised patients. *Cryptosporidium* parasites usually invade the small bowel, but in immunocompromised hosts, the large bowel and extraintestinal sites are also involved.

The parasite is transmitted by ingestion of oocysts excreted in the feces of infected animals and humans. The parasite is highly infectious, with an ID_{50} ranging from 9 to 1,042 oocysts, depending on the isolate *[468]*. Infection occurs when the ingested oocyst releases sporozoites, which attach to and invade the intestinal epithelial cells. The parasite has a predilection for the jejunum and terminal ileum *[468]*.

Person-to-person transmission is common in child care centers; infants with cryptosporidiosis diarrhea can infect adults during diapering *[469]*. Oocysts can contaminate recreational water sources (e.g., swimming pools, lakes) as well as public water supplies and may persist despite standard chlorination. Physical steps are necessary to remove the parasite from the water: flocculation, sedimentation, or filtration. Outbreaks have been associated with ingestion of contaminated drinking water in large metropolitan areas with chlorination but without filtration systems and with public swimming pools *[470]*. Foodborne and person-to-person spread also have been documented *[468]*. Cryptosporidiosis also occurs among international travelers. Although <4,000 cases were reported each year in the United States from 1995 to 2002, it is estimated that 300,000 persons are infected each year; underusage of diagnostic tests and poor sensitivity of the older tests combined with underreporting are the main reasons for this difference *[471]*. In industrialized countries, the prevalence of cryptosporidiosis among children is generally considered to be in the range of 3.0% – 3.6% *[472]*; it is reported more frequently among children in developing countries *[473-475]*.

Before the advent of effective antiretroviral therapy, cryptosporidiosis was diagnosed primarily in patients with advanced HIV disease and AIDS. However, the incidence has declined dramatically in areas where the use of HAART became widely available *[475, 476]*.

Microspora species are obligate, intracellular, spore-forming protozoa that primarily cause moderate-to-severe diarrhea among children. They are related to fungi but defined by their unique single polar tube that coils around the interior of the spore *[477]*. Many microsporidia were reported as pathogens in humans but *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common microsporidia that cause infection among patients with HIV infection. Other microsporidia like *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *P. ronneeafiei*, V*ittaforma* (*Nosema*) *corneae*, *Microsporidium* species, *Nosema ocularum*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, and *Anncaliia* (syns *Brachiola/Nosema*) *algerae* have been also implicated in human infections. The *Microspora* parasites develop in enterocytes and are excreted with feces and, like *C. parvum*, are transmitted by the fecal-oral route, which can include ingestion of contaminated food or water *[478]*. It causes infection in non-HIV-infected children, the elderly, travelers, and organ transplant recipients. Although the incidence of microsporidiosis has declined dramatically in areas where HAART is used, it continues to affect HIV-infected patients who are unable to receive or continue HAART.

Clinical Manifestations

Symptoms of cryptosporidiosis develop after an incubation period of 1 week. Frequent, usually nonbloody, watery, persistent diarrhea is the most common manifestation of both cryptosporidial and microsporidial infection, with abdominal cramps, fatigue, vomiting, anorexia, weight loss, and poor weight gain. Fever and vomiting are relatively common in children, mimicking viral gastroenteritis *[473]*. In almost half of the cases, the diarrhea persists for >2 weeks *[479]*. Longer episodes of diarrhea were associated with increased risk for recurrent episodes and weight loss *[480]*. Among immunocompromised children, chronic severe diarrhea can result in malnutrition, failure to thrive, and substantial intestinal fluid losses, resulting in severe dehydration and even death. Clinical history or physical examination does not allow differentiation of cryptosporidial or microsporidial disease from those caused by other pathogens.

Cryptosporidium can migrate into the bile duct and result in inflammation of the biliary epithelium, causing acalculous cholecystitis and sclerosing cholangitis *[481]*. Symptoms include fever, right upper abdominal pain, and elevated alkaline phosphatase. Pancreatitis can also rarely occur. Although infection is usually limited to the GI tract, pulmonary or disseminated infection can also occur among immunocompromised children.

The most common manifestation of microsporidiosis is GI tract infection. In addition to the more common acute and chronic diarrhea, microsporidia species have been described as causing hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, respiratory disease, sinusitis, encephalitis, and disseminated disease *[482]*. Different infecting species may result in different clinical syndromes. *Enterocytozoon bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *Encephalitozoon cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *Encephalitozoon* (syn *Septata*) *intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjuctivitis. *Encephalitozoon hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Because *Cryptosporidium* cannot be grown on laboratory media, diagnosis of cryptosporidiosis is usually made by microscopic identification of the oocysts in stool or tissue. Stool samples are concentrated using the sucrose flotation or formalin-ethyl acetate method; stained (using a modified Kinyoun acid-fast stain); and examined for small (4 – 6 μm in diameter), acid-fast positive oocysts. Unfortunately, this method is insensitive and requires >500,000 oocysts/mL of stool *[483]*. Monoclonal antibody-based fluorescein-conjugated stain for oocysts and an EIA to detect antigen in stool are preferred to staining methods because of enhanced sensitivity and specificity *[484]*. Antigen-detection assays (e.g., ELISA, immunochromatography) are available commercially with good sensitivity and excellent specificity *[484, 485]*. Molecular methods such as PCR hold promise to further enhance sensitivity *[486]*. Among persons with profuse diarrheal illness, a single stool specimen is usually adequate for diagnosis. However, oocyst excretion can be intermittent; therefore, the parasite might not be detected in every stool and among persons with milder disease, repeat stool sampling is recommended. Organisms can also be identified on small intestinal biopsy or intestinal fluid samples.

For diagnosis of microsporidia infection, thin smears of unconcentrated stool-formalin suspension or duodenal aspirates can be stained with modified trichrome stain. Chemofluorescent agents such as chromotrope 2R, calcofluor white (a fluorescent brightener), and Uvitex 2B (a fluorescent brightener) are useful as selective stains for microsporidia in stool and other body fluids. Microsporidia spores are small

(1 – 5 μm in diameter), ovoid, stain pink to red with modified trichrome stain, and contain a distinctive equatorial-belt-like stripe.

Urine sediment examination by light microscopy can be used to identify microsporidia spores causing disseminated disease (e.g., *Encephalitozoonidae*, *Trachipleistophora*). Transmission electron microscopy or PCR (using specific primers) is needed for speciation.

Endoscopy biopsy should be considered for all patients with chronic diarrhea of >2 months duration and negative stool examinations. Touch preparations are useful for rapid diagnosis (i.e., within 24 hours). Sensitive assays using PCR amplification of parasite DNA sequences extracted from stool or biopsy specimens have been developed for *Cryptosporidium* and *Enterocytozoon bieneusi [486, 487]* but are research tools and not commercially available.

Prevention Recommendations

Preventing Exposure

Caregivers and HIV-infected children should be educated and counseled concerning the different ways that *Cryptosporidium* can be transmitted. Modes of transmission include direct contact with fecal material from adults, diaper-aged children, and infected animals; contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Hand-washing after exposure to potentially fecally contaminated material, including diapers, is important in reducing the risk of *Cryptosporidium*. HIV-infected children should not be allowed contact with ill pets or stool from pets, particularly dogs and cats <6 months of age; stray pets; or surfaces contaminated with human or animal stool. Direct contact with calves and lambs at farms or petting zoos should be avoided for HIV-infected children.

HIV-infected children should not be allowed to drink water directly from lakes or rivers, including swallowing water while swimming or playing in recreational water. Caregivers and HIV-infected children should be aware that lakes, rivers, salt-water beaches, certain swimming pools, recreational water parks, and ornamental water fountains might be contaminated with human or animal waste that contains *Cryptosporidium*.

Some outbreaks of cryptosporidiosis have been linked to consuming water from municipal water supplies. During outbreaks or in other situations in which a community advisory to boil water is issued, boiling water for ≥3 minutes will eliminate the risk for cryptosporidiosis and should be done for preparing infant formula as well as for drinking water.

Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., can be stored unrefrigerated on grocery shelves) are also safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe water source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption might be either fresh (i.e., unpasteurized) or heat treated (i.e., pasteurized); only those juices labeled as pasteurized should be considered free of risk from *Cryptosporidium*. Other pasteurized beverages also are considered safe to drink.

Cryptosporidium-infected patients should not work as food handlers, especially if the food to be handled is intended to be eaten without cooking.

In a hospital, standard precautions (i.e., use of gloves and hand-washing after removal of gloves) should be

sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person. However, because of the potential for fomite transmission, some experts recommend that severely immunocompromised HIV-infected patients should not share a room with a patient with cryptosporidiosis **(CIII)**.

Similar to precautions for prevention of cryptosporidiosis, general attention to hand-washing and other personal hygiene measures will reduce exposure to microsporidia as well.

Preventing First Episode of Disease

Because chronic *Cryptosporidium* infection occurs most frequently in HIV-infected individuals with advanced immune deficiency, antiretroviral treatment of HIV-infected children prior to the development of severe immune deficiency is a primary modality of prevention.

Some observational studies from the pre-HAART era suggested that rifabutin or clarithromycin prophylaxis for MAC may be associated with decreased rates of cryptosporidiosis *[488, 489]*. However, the data are conflicting and insufficient to recommend using these drugs solely for prophylaxis of cryptosporidiosis. No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Immune reconstitution resulting from HAART will frequently result in clearance of *Cryptosporidium* and *Microsporidium* infections. Effective HAART is the primary initial treatment for these infections in HIV-infected children and adults *[476, 490]* **(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)**.

Cryptosporidium

No consistently effective therapy is available for cryptosporidiosis and duration of treatment among HIV-infected persons is uncertain *[491]*. Multiple agents have been investigated in small randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *C. parvum* has yet been shown consistently effective and durable when used alone without concomitant antiretroviral therapy *[491]*.

A review of clinical trials of treatment of *Cryptosporidia* in immunocompromised patients, including those with HIV infection, by the Cochrane Collaboration found that no agent has proven efficacy for the treatment of cryptosporidiosis among immunocompromised patients; however, in immunocompetent individuals, nitazoxanide reduces the load of parasites. Given the seriousness of this infection among immunocompromised individuals, use of nitazoxanide can be considered in immunocompromised HIV-infected children in conjunction with HAART for immune restoration *[491]* **(CIII)**.

Nitazoxanide is approved in the United States for treatment of diarrhea caused by *Cryptosporidium* and *Giardia lamblia* among children and is available in a liquid and tablet formulation (**BI** for HIV-uninfected and **CIII** for HIV-infected children). An Egyptian clinical trial among 100 HIV-uninfected adults and children randomized patients to a 3-day course of nitazoxanide or placebo *[492]*. 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 malnourished children aged 12 – 35 months (half HIV infected) reported a clinical response of 56% with treatment compared to 23% with placebo among HIV-uninfected children, but among HIV-infected children with low CD4 counts, the drug was no more effective than placebo *[493]*. These results may be due to the short course (3 days) of therapy as retreatment for additional 3 days increased the number of responders. In a study among HIV-infected adults who had CD4 counts >50 cells/mm^3, 14 days of nitazoxanide resulted in 71% (10 of 14) response using 500 mg twice daily and 90% (9 of 10) using 1,000 mg twice daily, compared with 25% with placebo *[494]*. The recommended dose for children is 100 mg orally twice daily for children aged 1 to 3 years and 200 mg twice daily for children aged 4 to 11 years. A tablet preparation (500 mg twice daily) is available for children aged ≥12 years. All medications should be given with food.

Paromomycin is a nonabsorbable aminoglycoside indicated for the treatment of intestinal amebiasis that is effective for treatment of cryptosporidiosis in animal models but is not specifically approved for cryptosporidiosis. A Cochrane Review and a meta-analysis of the two randomized controlled trials comparing paromomycin with placebo among adults with AIDS found the drug was no more effective than placebo at reducing diarrheal frequency or parasite burden *[491, 495, 496]*, and a clinical response to paromomycin is rare in patients with CD4 count <100 cells/mm^3. Therefore, data do not support a recommendation for the use of paromomycin for cryptosporidiosis **(DII)**.

Azithromycin has demonstrated some activity against *C. parvum* infection in a limited number of HIV-infected children *[497]*. An azithromycin regimen of 10 mg/kg/day on Day 1, and 5 mg/kg/day on Days 2 to 10 was successful in rapidly resolving enteric symptoms in three of four HIV-infected children with cryptosporidiosis *[497]*. However, data are insufficient to recommend use of this drug to treat cryptosporidial infection **(CIII)**.

Microsporidium

Albendazole has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *V. corneae [498, 499]*. Albendazole decreased diarrhea, sometimes with eradication of the organism in some studies *[497, 499]*. Albendazole is recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII)**.

No specific therapeutic agent is available for *Enterocytozoon bieneusi* infection. Fumagillin® (Sanofi-Synthelabo Laboratories, Gentilly, France), a water-insoluble antibiotic made by *Aspergillus fumigatus*, or its synthetic analog TNP-470 *[500]* have been shown to have anti-microsporidial activity and have 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 *[500]*. No data are available on use of fumagillin or TNP-470 among HIV-infected children, and neither drug is available in the United States. Data are insufficient to make recommendations on use of these drugs in children **(CIII)**. One report indicated that treatment with nitazoxanide for 60 days might resolve chronic diarrhea caused by *Enterocytozoon bieneusi* in the absence of antiretroviral therapy *[501]*, but this effect was minimal among patients with low CD4 counts, and therefore may be of limited utility **(CIII)**.

Keratoconjunctivitis caused by microsporidia among HIV-infected adults responds to topical therapy with investigational fumagillin eye drops prepared from Fumidil-B® (fumagillin bicylohexylammonium, a commercial product used to control a microsporidial disease of honeybees) in saline (to achieve a concentration of 70 µg/mL of fumagillin) *[502]* **(BII)**. The combination of albendazole and fumagillin has demonstrated consistent activity against microsporidia *in vitro* and is recommended for ocular infections, in addition to topical therapy, as microsporidia may remain present systemically despite clearance from the eye with topical therapy alone *[503]* **(BIII)**.

Metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis **(DII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In patients who are severely ill, total parenteral nutrition may be indicated **(CIII)**.

Nitazoxanide has not been associated with substantial side effects. Albendazole side effects are rare but hypersensitivity (e.g., rash, pruritis, fever), neutropenia (reversible), CNS effects (e.g., dizziness, headache), GI disturbances (e.g., abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Dose-related bone marrow toxicity is the principal adverse effect of fumagillin, with reversible thrombocytopenia and neutropenia being the most frequent adverse events; topical fumagillin has not been associated with substantial side effects.

IRIS has not been described in association with treatment of cryptosporidiosis or with treatment for *E. bieneusi* or non-*E. bieneusi* microsporidiosis.

Management of Treatment Failure

The only feasible approaches to management of treatment failure are supportive treatment and optimizing antiretroviral therapy to achieve full virologic suppression **(AIII)**.

Prevention of Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis or microsporidiosis. However, treatment for ocular microsporidiosis should be continued indefinitely because recurrence or relapse might follow treatment discontinuation **(BIII)**.

Discontinuing Secondary Prophylaxis

Not applicable.

Malaria

Epidemiology

Malaria is an acute and chronic disease caused by obligate, intracellular protozoa of the genus *Plasmodium*. Four species of *Plasmodium* are responsible for nearly all human infections: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. The majority of infections in the United States are caused by *P. falciparum* (60%) and *P. vivax* (25% – 30%) *[504]*. In the United States, 1,200 to 1,400 cases of malaria are imported annually, with 70% being acquired in Africa, 15% in Asia, and 15% in Latin America and the Caribbean *[504]*.

Most malaria (80%) becomes symptomatic within 30 days of arrival in the United States, and 99% within 1 year. Typically, 75% of U.S. travel-associated malaria cases have not taken any appropriate malaria chemoprophylaxis. Approximately 50% of infections among U.S. citizens are acquired by visiting friends and relatives (VFR) in malaria-endemic regions *[504]*. U.S.-born children of immigrants returning to visit family are at highest risk of death due to malaria. Greater than one-third of malaria cases among children are in newly arriving immigrants *[505-507]*.

This section will address malaria in HIV-exposed or infected children in the United States only and will not discuss malaria prophylaxis of children in malaria-endemic areas of the world. There are no reliable data on the prevalence of HIV infection among immigrant and refugee children resettling in the United States, since children aged <15 years are exempt from mandatory screening. It would be assumed that the underlying HIV prevalence rates in children relocating to the United States would be reflective of the overall rates of HIV in the migrating population. For example, Somali refugees have very low rates of HIV while Central and West African rates are substantially higher. Presumably, children at risk of coinfection with HIV and malaria, particularly asymptomatic individuals or those with unrecognized disease, would be highest in populations where the underlying prevalence of HIV and malaria are both excessive (i.e., West, Central, and portions of East Africa).

Clinical Manifestations

In contrast to data suggesting increased frequency of both parasitemia and clinical malaria in HIV-infected adults *[508, 509]*, studies in young children in malaria-endemic areas have generally not found an increase in frequency or density of parasitemia with HIV infection *[510-516]* with one exception, which suggested higher parasite density in children aged <5 years with HIV infection compared to HIV-uninfected children *[517]*. Additionally, most studies have not found malarial episodes to be more frequent or to present differently in HIV-infected than -uninfected children *[510, 512]*, although one study found that HIV-infected children aged >1 year may be more likely to have severe or complicated malaria *[515]*. A study in Kenya suggested that HIV-exposed children aged <2 years (regardless of their infection status) were more likely to have severe anemia with malarial episodes than children without HIV exposure *[516]*. Published studies have focused on younger HIV-infected children, and whether older HIV-infected children will behave more like HIV-infected adults is not known. In a study in Uganda, HIV-infected individuals aged ≥5 years with lower CD4 counts (<200 cells/mm^3) had higher parasite counts during clinical malaria *[517]*.

The signs and symptoms of malaria are varied and are highly dependent upon previous exposure (partial immunity), age of onset, and the species of the infecting organism and do not differ by HIV infection status in children. Fever is the most common symptom. In children, nonspecific symptoms predominate and may include chills, sweating, headache, myalgias, malaise, nausea, vomiting, diarrhea, and cough *[504, 518]*. These other common symptoms increase the potential for misdiagnosis as a viral syndrome,

upper respiratory tract infection, or gastroenteritis. In nonendemic settings, two-thirds of all children with malaria will initially be misdiagnosed and have two to four clinical visits prior to diagnosis *[507]*.

Beyond 30 days of leaving a malarious region, 75% of reported clinical malaria cases are caused by non-*P. falciparum* malaria species. Therefore, in nonimmune individuals, most malaria diagnosed >30 days after return, or travel to, the United States will be non-*P. falciparum*.

In contrast, the epidemiology in partially immune children may vary considerably. One study found that 60% of children migrating from holoendemic malarial regions were smear positive for *P. falciparum* 1 month after arrival in the United States *[519]*. Since these data were collected, the CDC has issued guidance to organizations resettling refugees to the United States to presumptively treat all refugees from sub-Saharan Africa, except under special circumstances, prior to departure for the United States. This treatment should decrease malaria rates in the future among refugees but does not completely eliminate risk because predeparture treatment with drugs effective against the blood stage does not eliminate liver stage parasites. However, nonrefugee immigrants from similar areas do not receive this presumptive therapy and are at greater risk of developing clinical manifestations of malaria after arrival in the United States. Therefore, children who have recently migrated from highly endemic malaria regions should either be presumptively treated for malaria or have post-arrival testing for malaria infection. CDC guidance can be found at: **www.cdc.gov/ncidod/dq/health.htm**. Chronic symptoms of splenomegaly, fever, and thrombocytopenia are highly specific for malaria in immigrant children and need appropriate evaluation *[504, 520]*. Congenital malaria is a rare occurrence, but this should be considered as a diagnosis in febrile neonates whose mothers migrated from areas where malaria is endemic; however, empiric therapy should not be given to febrile neonates of recent immigrants *[504]*.

Diagnosis

The diagnosis of malaria is based on the microscopic examination of a patient's blood. A thick blood smear is the most sensitive smear technique for detecting infection but is generally unhelpful in speciating the organism. Giemsa-stained thin blood smear gives the malaria parasites a distinctive appearance that usually allows accurate parasite speciation. In nonimmune persons, symptoms may develop before parasitemia is detectable. For this reason, several blood smear examinations taken at 12 − 24 hour intervals may be needed to positively rule out a diagnosis of malaria in a symptomatic patient. The sensitivity and specificity of blood smear are highly dependent on the operator's skills. Assistance with microscopic diagnosis of malaria is available through state public health departments and the CDC's Division of Parasitic Diseases diagnostic service (**http://www.dpd.cdc.gov/**).

Although blood smear examination remains the gold standard for laboratory confirmation of malaria, the Binax Now® Malaria Test, a rapid malaria antigen capture assay, has been approved by the FDA for use in clinical diagnosis of symptomatic malaria. It is approved for use in children and adults. This test, which utilizes a monoclonal antibody to histidine-rich protein 2 to detect *P. falciparum* and a monocloncal antibody aldolase to detect all malaria species, can be performed within 15 minutes. The studies presented to the FDA show specificity approaching 100% for all malaria and a sensitivity of >95% for *P. falciparum* and 85% – 95% for *P. vivax*. There are indications, however, that sensitivity for *P. ovale*, a less common form of human malaria, likely does not exceed 70%. Although this test has been shown to perform well in symptomatic individuals, preliminary data suggest poor performance of rapid diagnostic tests, including the Binax Now® Malaria Test, for screening asymptomatic individuals for malaria *[521, 522]*. Similarly, among asymptomatic immigrants, the sensitivity of a single blood smear is relatively poor (<50%) *[521, 522]*. Specific guidelines for laboratory diagnosis are summarized elsewhere and are available at CDC's malaria Web site (**http://www.cdc.gov/malaria/**).

Prevention Recommendations

Preventing Exposure

HIV-infected children, particularly those with immunosuppression, should be advised to use personal protective measures to prevent mosquito bites if traveling to endemic areas *[515]*. Specifically, clothing can be impregnated with permethrin, effective for weeks even through 10 washings **(AI)**. Long-acting DEET mosquito repellents (30% − 50% concentration) are very practical and 99% effective when combined with permethrin-treated clothing **(AI)**. DEET should be applied onto young children by caregivers and generally should not be applied to young children's hands **(AIII)**. Specific instructions by providers on product purchasing and use are invaluable. Insecticide treated bed nets are inexpensive and readily available in endemic countries. All children, regardless of their HIV-status, should sleep under an insecticide treated bed net when traveling in malaria-endemic areas.

Primary Prophylaxis

U.S.-born children of immigrant parents traveling to endemic regions are at especially high risk of acquiring malaria *[523]*. Child immigrants or second-generation immigrant children whose caregivers are from malaria-endemic areas are likely to travel to high-risk destinations and be more susceptible than their caregivers due to lack of previous malaria exposure **(AII)**. These children and their caregivers are at especially high risk of acquiring malaria. Children who will be traveling to malaria-endemic regions should receive pretravel counseling on insect avoidance techniques and receive appropriate chemoprophylaxis *[524, 525]*. Recommendations for chemoprophylaxis are the same for HIV-infected persons as for noninfected persons and are available at the CDC's Web site (**http://www.cdc.gov/malaria/**).

There is the potential for antiretroviral and antimalarial drug-drug interactions. Specifically, mefloquine significantly decreases steady-state ritonavir area under the curve plasma levels by 31%. In children receiving a boosted PI regimen with pre-existing moderate resistance, this decrease may indeed be significant. In addition, antimalarial medications may need special preparation and some are not easily delivered to children. Therefore, it is advisable that patients planning to travel to malaria-endemic areas visit a travel medicine specialist with training and experience in pediatrics ≥2 weeks prior to departure **(AII)**.

In nonholoendemic areas, there is some protection with TMP-SMX prophylaxis in combination with the use of bed nets, resulting in >90% reduction in clinical malaria in one study *[526]*. However, TMP-SMX is not recommended as an antimalarial prophylactic regimen by the CDC, and HIV-infected travelers must not rely on TMP-SMX for chemoprophylaxis against malaria.

Discontinuing Primary Prophylaxis

Travel-related chemoprophylaxis with chloroquine, mefloquine, and doxycycline is generally discontinued 4 weeks after leaving a malaria-endemic area since these drugs are not effective against the developing malaria in the liver and only kill the malaria once it has emerged to infect the red blood cells. Atovaquone-proguanil is discontinued 1 week after leaving malaria-endemic areas. Chemoprophylaxis is not 100% effective, and malaria should be included in the differential diagnosis of anyone having traveled in the previous 12 months to a malaria-endemic area who presents with fever or other signs or symptoms consistent with malaria.

Treatment Recommendations

Treatment of Disease

Treatment of malaria is based on the severity of disease, age of onset, malaria species, and known resistance patterns **(AI)**. It is unclear whether there is a difference in response to antimalarial treatment in relation to HIV infection status. HIV-infected or -exposed children are frequently excluded from drug efficacy trials because of cotrimoxazole prophylaxis. Current published studies have conflicting results, have used older antimalarials, or were not adequately powered to answer this question *[527, 528]*. HIV infection status should not affect choice of therapy and there are currently no recommendations for alternative dosing of antimalarial drugs in HIV-infected individuals **(AII)**. A full discussion of treatment in children is beyond the scope of this document but has been addressed elsewhere *[529]*. Treatment dosing for adolescents and children is provided in Table 4. In addition, up-to-date malaria treatment recommendations are available from the CDC at **http://www.cdc.gov/malaria/pdf/treatmenttable.pdf**.

P. falciparum

Uncomplicated chloroquine-sensitive *P.falciparum* malaria should be treated with chloroquine. The recommended treatment options for uncomplicated chloroquine-resistant *P. falciparum* in the United States are: atovaquone-proguanil (Malarone™), quinine with clindamycin or doxycycline (in children aged ≥8 years), or mefloquine (Lariam™) **(AI)**. For dosages, refer to the CDC Web site mentioned above. It is imperative that the clinician choose a medication according to known sensitivity patterns from the area where the malaria was acquired.

The current drug of choice for uncomplicated chloroquine-resistant *P. falciparum* malaria is atovaquone-proguanil, which is FDA approved for use in children weighing >5 kg, is well tolerated, has a wide therapeutic window, and provides simple dosing with pediatric tablets available. Although mefloquine is FDA approved for ages >6 months, pediatric tablets are not available. However, mefloquine is the only treatment choice for uncomplicated chloroquine-resistant *P. falciparum* malria in children weighing <5 kg.

Severe *P. falciparum* should be treated with intravenous quinidine gluconate (or intravenous quinine when available). Duration of quinine/quinidine therapy is typically 3 days with clindamycin, or doxycycline, continued for 7 days **(AI)**. Intravenous quinidine can cause hypoglycemia, ventricular arrhythmia, and QT prolongation; therefore close monitoring, including telemetry, is required during infusion. Increasingly, quinidine is not always stocked by hospital pharmacies. Ritonavir inhibits quinidine metabolism and is considered a contraindication. An alternative is artesunate, which is available from the CDC on an investigational new drug (IND) protocol *[530]*. When there are signs or symptoms of severe disease, especially when there are indicators of a poor prognosis (including clinical features of impaired level of consciousness, respiratory distress, jaundice, seizures, or shock or laboratory features of hypoglycemia, elevated bilirubin, acidosis, elevated liver aminotransferase levels, or renal insufficiency), a tropical medicine specialist should be consulted. For artesunate release or additional assistance, contact the 24-hour CDC malaria hotline at 770-488-7788 during the day and 770-488-7100 after hours, weekends, and holidays.

P. vivax, P. ovale, P. malariae

The medication of choice for non-*P. falciparum* malaria is chloroquine; the organisms are generally sensitive to this drug **(AI)**. Chloroquine is generally well tolerated. The most common reaction is self-limited itching (2%), especially in persons of African descent (50%); this is not an allergy and should not be considered a contraindication to treatment with chloroquine. However, there are exceptions where *P. vivax* has known high rates of chloroquine resistance, most notably in New Guinea. A patient infected with known or suspected chloroquine-resistant *P. vivax* malaria should receive an alternative first-line

agent (i.e., quinine plus clindamycin or doxycycline, atovaquone-proguanil, mefloquine). Both *P. vivax* and *P. ovale* have an intrahepatic stage (hypnozoite) that is not treated with the acute blood stage medications mentioned. In order to prevent relapse of *P. vivax* or *P. ovale* infection, patients should receive presumptive antirelapse therapy with primaquine following the primary blood stage treatment **(AI)**. Glucose-6-phosphate dehydrogenase deficiency **must** be excluded prior to any primaquine use due to the risk of severe hemolytic anemia.

Unknown Species Type

When reliable identification of the malaria species is not possible or in a severely ill individual, clinicians should always treat for the worst case scenario of chloroquine-resistant *P. falciparum* malaria **(AIII)**. PCR assays are now commercially available and can be used to speciate when microscopy is not sufficient. Assistance with speciation is also available from state public health departments and the CDC's Division of Parasitic Diseases diagnostic service (**http://www.dpd.cdc.gov/**). After completion of initial therapy, knowing the malaria species is important since presumptive antirelapse therapy is necessary for *P. ovale* and *P. vivax*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Severe malaria commonly induces hypoglycemia in children, especially when treated with intravenous quinine/quinidine due to the inhibition of gluconeogenesis and induction of endogenous insulin production. Therefore, it is prudent to use a crystalloid solution containing glucose for fluid maintenance while closely monitoring glucose levels until intravenous quinine/quinidine therapy has been completed. Monitoring glucose is especially important for infants and individuals with altered mental status. Cardiac and intensive care monitoring is recommended as quinine/quinidine can cause hypotension and may widen the QRS interval. Another common adverse reaction (50% − 75%) to quinine is tinnitus, although this generally resolves following treatment.

Management of Treatment Failure

Treatment failure with *P. falciparum* among children receiving a full course of appropriate antimalarial therapy is uncommon but may occur. Patients should be monitored for clinical response as well as for signs of recrudescence after therapy completion. Current published studies do not have the power to detect a difference in treatment outcomes in HIV-infected compared to HIV-uninfected children *[527, 528]*. Relapse of *P. vivax* and *P. ovale* can occur from the dormant (hypnozoite) liver form but is less common if primaquine treatment is given. Malaria medications purchased in sub-Saharan Africa or Southeast Asia may be counterfeit *[531]*.

Prevention of Recurrence

With the exception of reactivation of *P. vivax* and *P. ovale* hypnozoites, malaria, once successfully treated, does not recur. Malaria infection does not infer protective immunity and continued exposure to malaria parasites can result in repeated infection.

Discontinuing Secondary Prophylaxis

Not applicable.

Toxoplasmosis

Epidemiology

The major mode of transmission of *Toxoplasma gondii* infection among infants and young children is congenital, occurring almost exclusively among neonates born to women who sustain primary *Toxoplasma* infection during pregnancy. The incidence of congenital toxoplasmosis in the United States is an estimated 1 case per 1,000 – 12,000 live-born infants *[532, 533]*. The seroprevalence of *T. gondii* in U.S.-born persons aged 12 to 49 years in the United States declined from 14.1% during the National Health and Nutrition Examination Survey (NHANES) 1988 – 1994 to 9.0% during NHANES 1999 – 2004 *[534]*. Older children, adolescents, and adults typically acquire *Toxoplasma* infection by eating poorly cooked meat that contains parasitic cysts or by unintentionally ingesting sporulated oocysts in soil or contaminated food or water *[535]*.

The overall risk for maternal-fetal transmission in women without HIV infection who acquire primary *Toxoplasma* infection during pregnancy is 29% (95% CI 25% – 33%) *[536]*. The risk for congenital infection is low among infants born to women who become infected during the first trimester (range: 2% – 6%) but increases sharply thereafter, with a risk as high as 81% for women acquiring infection during the last few weeks of pregnancy *[536, 537]*. Infection of the fetus in early gestation usually results in more severe disease, compared with milder disease when infection occurs late in gestation.

The prevalence of latent *Toxoplasma* infection among women with and without HIV infection in the United States was assessed in a cross-sectional study of 2,525 nonpregnant women enrolled in the Women's Interagency Health Study *[538]*. The prevalence of *Toxoplasma* seropositivity was 15% and did not differ by HIV infection status. A few cases of mother-to-infant transmission of *Toxoplasma* in HIV-infected women have been reported *[539-543]*. Prenatal transmission of *Toxoplasma gondii* from women without HIV infection who have chronic *Toxoplasma* infection acquired before pregnancy is rare *[544]*. However, in the setting of HIV coinfection, perinatal transmission of *Toxoplasma* has been observed among women with chronic *Toxoplasma* infection (transmission rate: <4%), presumably because of reactivation of replication of the organism among women with severe immune suppression *[539-542]*.

Infection of the CNS with *Toxoplasma gondii* was reported as an AIDS-indicator condition in <1% of pediatric AIDS cases before the advent of HAART *[545]*. In the HAART era, this condition is rarely encountered in children with HIV infection in the United States. Development of CNS toxoplasmosis in children with HIV infection in the HAART era occurred in only 0.2% (5 of 2,767) of those enrolled in the long-term follow-up study PACTG 219c *[3]*. In most cases of *Toxoplasma* encephalitis (TE) among HIV-infected children, infection is considered to have occurred *in utero*. More rarely, it has also been reported among older HIV-infected pediatric patients, presumably with primary acquired toxoplasmosis *[546-548]*. As in adults, the greatest risk would be among severely immunosuppressed children (e.g., CD4 count <50 cells/mm^3).

Clinical Manifestations

In studies of non-immunocompromised infants with congenital toxoplasmosis, the majority of infants (70% – 90%) are asymptomatic at birth. However, the majority of asymptomatic children develop late sequelae (e.g., retinitis, visual impairment, and intellectual or neurologic impairment) with the interval until the onset of their symptoms ranging from several months to years. When symptoms do occur in newborns, either of two presentations can be observed: generalized disease or predominantly neurologic disease. Symptoms can include maculopapular rash; generalized lymphadenopathy; hepatosplenomegaly; jaundice; hematologic abnormalities, including anemia, thrombocytopenia, and neutropenia; and

substantial CNS disease, including hydrocephalus, intracerebral calcification, microcephaly, chorioretinitis, and seizures *[549]*.

Similarly, toxoplasmosis acquired after birth is most often initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly.

TE should be considered among all HIV-infected children with new neurologic findings. Although focal findings are more typical, the initial presentation can be variable and reflect diffuse CNS disease. Other symptoms include fever, reduced alertness, and seizures.

Isolated ocular toxoplasmosis is rare and usually occurs in association with CNS infection. As a result, a neurologic examination is indicated for children who have had *Toxoplasma* chorioretinitis diagnosed. Ocular toxoplasmosis appears as white retinal lesions with little associated hemorrhage; visual loss might be observed initially.

Less frequently observed presentations among HIV-infected children with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis *[542, 550]*.

Diagnosis

HIV-infected women might be at increased risk for transmitting *Toxoplasma gondii* to their fetuses, and serologic testing for *Toxoplasma* should be performed for all HIV-infected pregnant women. All infants whose mothers are both HIV-infected and seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis *[90]*. Congenital toxoplasmosis can be diagnosed by using EIA or an immunosorbent assay to detect the presence of *Toxoplasma*-specific IgM, IgA, or IgE in neonatal serum within the first 6 months of life, or persistence of specific IgG antibody beyond age 12 months *[551-554]*. IgA might be more sensitive for detection of congenital infection than IgM or IgE *[552]*. However, approximately 20% – 30% of infants with congenital toxoplasmosis will not be identified in the neonatal period with IgA or IgM assays *[553]*.

Serologic testing is the major method of diagnosis, but interpretation of available assays is often confusing and difficult. Using the services of a specialized reference laboratory that is capable of performing serology, isolation of organisms, and PCR and offers assistance in interpreting results, especially when attempting to diagnose congenital toxoplasmosis, can be helpful *[552]*.

Additional methods that can be used to diagnose infection in the newborn include isolation of the *Toxoplasma* parasite by mouse inoculation, or inoculation in tissue cultures of CSF, urine, placental tissue, amniotic fluid, or infant blood. *Toxoplasma gondii* DNA can be detected by PCR performed on body fluids (e.g., WBC, CSF, amniotic fluid, or tissues) in a reference laboratory *[552, 553]*. If a possible diagnosis of congenital toxoplasmosis at the time of delivery is uncertain, an evaluation of the neonate should be undertaken and should include ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and imaging of the head (either CT or magnetic resonance imaging [MRI] scans) to determine whether hydrocephalus or calcifications are present.

In the United States, routine *Toxoplasma* serologic screening of HIV-infected children whose mothers do not have toxoplasmosis is not recommended because of its low prevalence. However, in regions with high incidence of *Toxoplasma* infection, serologic testing might be selectively considered for HIV-infected children aged >12 months. HIV-infected adolescents without a history of previous *Toxoplasma* infection should undergo serologic testing.

A presumptive diagnosis of CNS toxoplasmosis is based on clinical symptoms, serologic evidence of infection, and the presence of a space-occupying lesion on imaging studies of the brain *[555]*. Cases of TE have rarely been reported in persons without *Toxoplasma*-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis. CT of the brain might indicate multiple, bilateral, ring-enhancing lesions in CNS toxoplasmosis, especially in the basal ganglia and cerebral corticomedullary junction. MRI is more sensitive and will confirm basal ganglia lesions in the majority of patients *[556]*. F-fluoro-2-deoxyglucose-positive emission tomography has been reported to be helpful in adults in distinguishing *Toxoplasma* abscesses from primary CNS lymphoma, but the accuracy is not high and this test is not widely available.

Definitive diagnosis of TE requires histologic or cytologic confirmation by brain biopsy, which might demonstrate leptomeningeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Brain biopsy is reserved by some experts for patients failing to respond to specific therapy.

Prevention Recommendations

Preventing Exposure

All HIV-infected children, adolescents, and their caregivers should be counseled regarding sources of *Toxoplasma gondii* infection. They should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison **(BIII)**. Specifically, lamb, beef, and pork should be cooked to an internal temperature of 165º F – 170º F *[557]*; meat cooked until it is no longer pink inside usually has an internal temperature of 165º F – 170º F and therefore, from a more practical perspective, satisfies this requirement. Hands should be washed after contact with raw meat and after gardening or other contact with soil; in addition, fruits and vegetables should be washed well before eating them raw **(BIII)**. Stray cats should not be handled or adopted; if there is a cat in the household, it is advised to keep the cat inside and the litter box should be changed daily, preferably by an HIV-negative, nonpregnant person **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis **(EII)**.

Preventing First Episode of Disease

Toxoplasma-seropositive adolescent and adult patients who have a CD4 count of <100 cells/mm^3 should be administered prophylaxis against TE **(AII)** *[434]*. Specific levels of immunosuppression that increase the risk of developing TE in children are less well defined. *Toxoplasma*-seropositive children with CD4 <15% should be administered prophylaxis against TE **(BIII)**. For children aged >6 years, the same absolute CD4 cell count level as for HIV-infected adults can be used **(BIII)**.

In HIV-infected adolescents and adults, the double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for PCP prophylaxis is effective against TE as well and is therefore recommended **(AII)** *[434]*. TMP-SMX, one double-strength tablet three times weekly (or 3 consecutive days a week), is an alternative **(BIII)**. There are limited data on the efficacy of TMP-SMX as a primary preventive agent for TE in children. However, based upon adult data, it is also the regimen of choice in children **(BIII)**; for pediatric dosage recommendations see Table 1. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which is also effective against PCP **(BI)** *[558, 559]*. Atovaquone with or without pyrimethamine also can be considered **(CIII)**. Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data **(DII)**. Aerosolized pentamidine does not protect against TE and is not recommended **(EI)** *[434, 435]*. *Toxoplasma*-seronegative adults and adolescents who are not taking a PCP-prophylactic regimen known to be active against TE should be retested for IgG antibody to *Toxoplasma* when their CD4 count declines to <100 cells/mm^3 to determine whether they have seroconverted and are therefore at risk for TE

(CIII). Severely immunosuppressed children who are not receiving TMP-SMX or atovaquone who are determined to be seropositive for *Toxoplasma* should be administered prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine) **(BIII)**.

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued among HIV-infected adult and adolescent patients who have responded to HAART with an increase in CD4 count to >200 cells/mm^3 for >3 months **(AI)**. Multiple observational studies *[446, 560, 561]* and two randomized trials *[562, 563]* have reported that primary prophylaxis can be discontinued with minimal risk for experiencing TE recrudescence among patients who have responded to HAART with an increase in CD4 count from <200 cells/mm^3 to ≥200 cells/mm^3 for >3 months. Although patients with CD4 counts of <100 cells/mm^3 are at greatest risk for experiencing TE, the risk for TE occurring when CD4 count has increased to 100 – 200 cells/mm^3 has not been studied as rigorously as an increase to >200 cells/mm^3. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/mm^3. Discontinuing primary TE prophylaxis is recommended because prophylaxis adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. There are no data on the safety of discontinuing primary TE prophylaxis for HIV-infected children whose CD4 percentage rises above 15%. Based upon adult data, it may be safe to discontinue TMP-SMX once a child responds to HAART with a sustained rise in their CD4 percentage above 15%; for children aged >6 years, the same CD4 count as for HIV-infected adults can be used **(CIII)**.

Prophylaxis should be reintroduced in HIV-infected adults and adolescents if CD4 count decreases to <100 – 200 cells/mm^3 **(AIII)** or CD4 percentage falls below 15% for HIV-infected children **(BIII)**.

Treatment Recommendations

Treatment of Disease

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. Although controversy exists regarding the efficacy of treatment of pregnant women with acute toxoplasmosis in an attempt to prevent infection of the fetus *[564]*, most experts would recommend such therapy *[90]*. 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)**. Absent definitive data, some experts would recommend treating HIV-infected infants longer than uninfected infants.

The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII)** *[549, 565]*. Although the optimal duration of therapy is undefined, the recommended duration of treatment of congenital toxoplasmosis for infants without HIV infection is 12 months *[565]* **(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 from months 7 to 12 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 CNS or ocular or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(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. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin **(AI)**. Azithromycin also has been used with pyrimethamine and leucovorin among sulfa-allergic adults instead of clindamycin, but this regimen has not been studied among children **(CIII)**.

Oother alternatives in adults are atovaquone 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)**. TMP-SMX alone has been used as an alternative to pyrimethamine-sulfadiazine among adults, but this has not been studied among children **(CIII)**.

For isolated ocular toxoplasmosis in non-immunocompromised hosts, TMP-SMX alone has been shown to be as effective as pyrimethamine-sulfadiazine *[566]*. However, these data have not been duplicated in HIV-infected persons and therefore this regimen cannot be recommended for this group of patients.

Corticosteroids (e.g., dexamethasone or prednisone) are recommended for children with CNS disease when 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.

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

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Children with TE should be routinely monitored for clinical and radiologic improvement and for adverse effects of treatment; changes in antibody titers are not useful for monitoring responses to therapy.

IRIS has been described only rarely in HIV-infected adults and has not been described in pediatric HIV-infected patients *[567]*.

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) always should 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, leukopenia, hepatitis, GI symptoms (e.g., nausea, vomiting, and diarrhea), and crystalluria. Clindamycin can be associated with fever, rash, and GI symptoms (e.g., nausea, vomiting, and diarrhea, including pseudomembranous colitis) and hepatotoxicity.

Drug interactions between anticonvulsants and antiretrovirals should be evaluated. Patients receiving corticosteroids should be closely monitored for development of other OIs.

Management of Treatment Failure

Brain biopsy should be considered when there is early clinical or radiologic neurologic deterioration despite adequate empiric treatment or among children who fail to clinically respond to anti-*Toxoplasma*

therapy after 10 to 14 days. For children who undergo brain biopsy and have confirmed histopathologic evidence of TE despite treatment, a switch to an alternative regimen as previously described should be considered **(BIII)**.

Prevention of Recurrence

Patients who have completed initial therapy for acquired TE should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI)** *[568, 569]* unless there is immune reconstitution with antiretroviral therapy. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective for this purpose **(AI)**. A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin **(BI)**; however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well **(AII)**. Based on adult data, atovaquone with or without pyrimethamine also can be considered for children **(CIII)**. Limited data support the use of TMP-SMX for secondary prophylaxis *[570]*; this regimen should only be used for persons not tolerant to pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CII)**.

Discontinuing Secondary Prophylaxis

Adult and adolescent patients receiving secondary prophylaxis for acquired TE are at low risk for recurrence of TE when they have successfully completed their initial therapy, remain asymptomatic with regard to signs and symptoms of TE, and have a sustained increase in their CD4 count of >200 cells/mm^3 after HAART (e.g., >6 months) *[560, 561, 563, 571, 572]*. Discontinuing chronic maintenance therapy in HIV-infected adolescents and adults who meet these criteria is a reasonable consideration **(BI)**. It appears that the highest risk for relapse occurs within the first 6 months of stopping secondary prophylaxis. Certain specialists would obtain an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate. The safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied extensively. However, given the data in adults, clinicians caring for HIV-infected children aged <6 years can consider discontinuing secondary prophylaxis against *Toxoplasma gondii* after they have completed TE therapy and are asymptomatic and once the CD4 percentage has risen above 15% for ≥6 months on stable HAART; for children aged >6 years, the same CD4 count used in adults (CD4 >200 cells/mm^3) can also be used **(BIII)**. Prophylaxis should be reinstituted if these parameters are not met.

VIRAL INFECTIONS:
Cytomegalovirus

Epidemiology

Infection with human cytomegalovirus (CMV) is common and usually inapparent; acquisition of CMV can occur during infancy, early childhood, or adolescence. Transmission can occur vertically from an infected woman to her offspring; horizontally by contact with virus-containing breast milk, saliva, urine, or sexual fluid; or through transfusion of infected blood or transplantation of infected organs. In infancy and early childhood, infection usually occurs secondary to ingestion of infected breast milk or exposure to infected saliva or urine. Infection occurs at younger ages in locations where sanitation is less optimal. Among adolescents, sexual transmission is the major mode of CMV acquisition.

Age-related prevalence of infection varies widely, depending on living circumstances and social customs. Breastfeeding, child-rearing practices, crowding, sanitation, and sexual behavior probably all influence age-related variations in CMV prevalence. Where rates of maternal seropositivity are high and breast feeding is common, more than half of infants acquire CMV during the first year of life *[573]*. Group care of children facilitates the spread of CMV, especially in toddlers, and leads to higher prevalence of infection in those who attend daycare centers and in their caregivers *[574, 575]*. In Africa, Asia, and Latin America, the majority of children are infected by CMV prior to adolescence. In the United States and Western Europe, the prevalence of antibody to CMV in adults from middle and upper socioeconomic strata is 40% – 60%, whereas that in low-income adults is ≥80% *[576]*. Overall among U.S. women of childbearing age, the prevalence of CMV infection is 50% – 80%, with the highest prevalence in women in lower socioeconomic strata *[577, 578]*. The prevalence of CMV infection among HIV-infected pregnant women is higher than in the general population, with approximately 90% of HIV-infected pregnant women being coinfected with CMV *[579, 580]*.

CMV is the most common congenitally transmitted infection, occurring in 0.2% – 2.2% of live-born infants in the United States *[581]*. Congenital (*in utero*) CMV infection occurs most commonly among infants born to women with primary CMV infection during pregnancy. Following primary infection during pregnancy, the rate of transmission to the fetus is approximately 30% – 40% *[577, 582]*. In comparison, the rate of congenital infection after nonprimary CMV infection generally has been believed to be significantly lower (range: 0.15% – 1.0%) *[581, 583, 584]*. More recent studies demonstrate that *in utero* transmission with nonprimary maternal infection can occur because of reactivation of infection among women infected before pregnancy or reinfection with a different CMV strain among women who are CMV seropositive *[585, 586]*; these studies are challenging the traditional understanding of transmission risk and clinical outcomes following nonprimary maternal CMV infection.

CMV also can be transmitted during the intrapartum or postpartum periods from mother to infant. Up to 57% of infants whose mothers shed CMV at or around the time of delivery become infected with CMV, and up to 53% of children who are breastfed with milk that contains infectious virus can become CMV infected. Symptomatic CMV disease in the infant is much less common when CMV is acquired intrapartum or through breastfeeding, occurring primarily in premature neonates.

HIV-infected women with CMV infection have a higher rate of CMV shedding from the cervix than women without HIV infection (52% – 59% compared with 14% – 35% in HIV-uninfected cohorts) *[587]*. The risk for mother-to-child transmission of CMV may be increased among infants born to women dually infected with CMV and HIV. In one study of 440 infants born to HIV-infected women in the United States, the overall rate of *in utero* infection was 4.5% *[11]*, higher than the <2% rate of *in utero* infection in the general U.S. population.

HIV-infected children appear to be at higher risk for acquisition of CMV infection during early childhood than children without HIV infection *[11]*. The rate of CMV acquisition in HIV-infected children appears to be particularly high during the first 12 months of life but continues to remain higher among HIV-infected than uninfected children through age 4 years as they become exposed to CMV infection in other children in child care or school settings.

CMV disease is less frequent among HIV-infected children than HIV-infected adults but contributes substantially to morbidity and mortality. In the pre-antiretroviral era, CMV caused 8% – 10% of pediatric AIDS-defining illness *[588]*. Data in HIV-infected adults has shown a 75% – 80% decrease in the incidence of new cases of CMV end-organ disease with the advent of antiretroviral therapy, with an incidence now estimated to be <6 cases per 100 person-years *[589]*. In a study of OIs in more than 3,000 children followed in PACTG studies in the pre-HAART era, the frequency of CMV retinitis was 0.5 cases per 100 child-years and of other CMV disease, 0.2 events per 100 child-years *[1]*. The event rate varied significantly by CD4 percentage; the incidence of CMV retinitis was 1.1 cases per 100 child-years in children with CD4 <15% compared to 0.1 per 100 child-years in children with CD4 >25%. In data from the same cohort in the HAART era, the overall rate of CMV retinitis was <0.5 per 100 child-years *[3]*. In the Perinatal AIDS Collaborative Transmission Study (PACTS), the incidence of nonocular CMV before and after January 1997 (pre- and post-HAART eras) was 1.4 per 100 child-years and 0.1 per 100 child-years, respectively *[4]*. Similarly, CMV retinitis declined from 0.7 to 0.0 per 100 child-years in the same period.

Symptomatic HIV-infected children with CMV coinfection have a higher rate of CMV viruria than asymptomatic HIV-infected or HIV-exposed children. Overall, one-third of HIV-infected children shed CMV (≤60% in children with AIDS) compared with 15% – 20% of CMV-infected, HIV-exposed but uninfected children and <15% of CMV-infected infants not exposed to HIV *[590]*.

Clinical Manifestations

Approximately 10% of infants with *in utero* CMV infection are symptomatic at birth with congenital CMV syndrome (CMV inclusion disease); mortality of children with symptomatic disease is as high as 30%. About half of neonates with symptomatic congenital CMV disease are small for gestational age; additional findings may include petechiae (76%), jaundice (67%), hepatosplenomegaly (60%), chorioretinitis (20%), microcephaly (53%), intracranial calcifications (55%), and hearing impairment (≤65%) *[591, 592]*. Approximately 90% of infants with symptomatic disease at birth who survive have late complications, including substantial hearing loss, mental retardation, chorioretinitis, optic atrophy, seizures, or learning disabilities *[577]*. Although the majority of children with *in utero* CMV infection do not have symptoms at birth, 10% – 15% are at risk for developing later developmental abnormalities, sensorineural hearing loss, chorioretinitis, or neurologic defects.

HIV-infected children with CMV coinfection appear to have accelerated progression of HIV disease compared with those without CMV infection *[11, 588, 593]*. In one study from the pre-HAART era, 53% of infants with HIV/CMV coinfection had progression to AIDS or death by age 18 months, compared with 22% of HIV-infected children without CMV infection; those with CMV coinfection also were more likely to have CNS (36% vs 9%). The relative risk for HIV disease progression in those with CMV coinfection compared with those without coinfection was 2.6 (95% CI 1.1 – 6.0) *[11]*.

CMV retinitis is the most frequent severe manifestation of CMV disease among HIV-infected children, accounting for approximately 25% of CMV AIDS-defining illnesses. CMV retinitis among young HIV-infected children is frequently asymptomatic and discovered on routine examination. Older children with CMV retinitis present similarly to adults with floaters, loss of peripheral vision, or reduction in central vision. Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates

and associated retinal hemorrhages. A more indolent, granular retinitis also may occur. HIV-infected children with CD4 counts <100 cells/mm^3 are more likely to develop CMV retinitis than those with higher CD4 counts; however, CD4 count is less predictive of risk for CMV disease in young infants, and systemic and localized CMV disease also can occur among HIV-infected infants with higher, age-adjusted CD4 counts *[590, 594]*.

End-organ CMV disease has been reported in the lung, liver, GI tract, pancreas, kidney, sinuses, and CNS *[594-597]*. In children with extraocular CMV disease, predominantly nonspecific symptoms (e.g., fever, poor weight gain, and loss of developmental milestones with laboratory abnormalities of anemia, thrombocytopenia, and elevated lactic dehydrogenase) are initially observed, although the extent to which CMV or HIV infection themselves are contributing to these findings is unclear *[590]*. GI manifestations among HIV-infected children include CMV colitis (the most common GI manifestation), oral and esophageal ulcers, hepatic involvement, ascending cholangiopathy, or gastritis. Odynophagia is a common presentation of CMV esophagitis, whereas abdominal pain and hematochezia frequently occur with CMV colitis. Sigmoidoscopy in CMV colitis is nonspecific, demonstrating diffuse erythema, submucosal hemorrhage, and diffuse mucosal ulcerations. Esophageal or colonic ulcerations may cause perforation or hemorrhage.

The role of CMV in pulmonary disease among HIV-infected children is difficult to assess because it is often isolated with other organisms (e.g., *P. jirovecii*). Histologic evidence of CMV disease is needed to determine if active disease is present. CMV pneumonia is an interstitial process with gradual onset of shortness of breath and dry, nonproductive cough; auscultatory findings may be minimal.

CNS manifestations of CMV include subacute encephalopathy, myelitis, and polyradiculopathy (primarily observed in adults but rarely reported among children). The subacute or chronic encephalopathy of CMV can be difficult to differentiate clinically from HIV dementia, with symptoms of confusion and disorientation attributable to cortical involvement. Focal signs can be attributed to lesions in the brainstem. CSF findings are nonspecific and may indicate a polymorphonuclear predominance (>50% of patients), elevated protein (75%), and low glucose (30%). However, up to 20% of children with CMV CNS involvement have completely normal CSF indices. CMV also can cause a rapidly progressive, often fatal CNS disease with defects in cranial nerves, nystagmus, and increasing ventricular size *[598]*.

Diagnosis

CMV infection versus disease can be difficult to differentiate in HIV-infected children. Because of transplacental transfer of antibody from mother to child, a positive CMV antibody assay in an infant aged <12 months can be indicative of maternal infection but not necessarily infection of the infant. In an infant aged >12 months, a positive CMV antibody assay indicates previous infection with CMV but not necessarily active disease. At any age, a positive CMV culture or PCR is indicative of infection, but not necessarily of disease.

CMV can be isolated in cell culture from peripheral blood leukocytes, body fluids (e.g., urine), or tissues. Using centrifugation-assisted shell vial culture amplification techniques, CMV can be detected within 16 to 40 hours of culture inoculation. A positive blood buffy-coat culture establishes a diagnosis of CMV infection and increases the likelihood that disease or symptoms were caused by CMV, because children with positive blood cultures are at higher risk for developing end-organ disease.

Different methods have been used to detect viral antigen or DNA directly and identify patients at risk for development of CMV disease, including detection of pp65 antigenemia, qualitative and quantitative PCR, and DNA hybridization. The DNA assays are more sensitive than buffy-coat or urine cultures for detecting CMV and can be used to identify patients at higher risk for development of clinically

recognizable disease. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV CNS disease. Quantitative DNA PCR can be used as a marker of risk for disease and to monitor response to therapy *[599]*.

Recovery of virus from tissues (e.g., endoscopically guided biopsies of GI or pulmonary tissue) provides evidence of disease in symptomatic patients. The limitation of this method is that it takes 1 to 6 weeks to detect visible cytopathic effects in cell culture. Staining of shell vial culture with CMV monoclonal antibodies or immunostaining for CMV antigens can allow earlier diagnosis of infection. Histopathology demonstrates characteristic "owl's eye" intranuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens; staining with CMV monoclonal antibodies or immunostaining for CMV antigens also can be done. The same procedures can be used on cells obtained from bronchoalveolar lavage.

Prevention Recommendations

Preventing Exposure

HIV-exposed infants and HIV-infected children, adolescents, and adults who are seronegative for CMV and require blood transfusion should be administered only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations **(BIII)**.

Beginning at 1 year of age, CMV antibody testing on an annual basis is recommended for CMV-seronegative HIV-infected infants and children who are severely immunosuppressed (e.g., CD4 count <100 cells/mm^3 or CD4 percentage <10%) **(BII)**. Annual testing will allow identification of children who have acquired CMV infection and might benefit from screening for retinitis.

HIV-infected adults and adolescents who are child care providers or parents of children in child care facilities should be informed that they are at increased risk for acquiring CMV infection **(BI)**. Risk for acquiring CMV infection can be diminished by optimal hygienic practices (e.g., hand-washing) **(AII)**.

Preventing First Episode of Disease

The primary method for preventing severe CMV disease is recognition of the early manifestations of the disease and prevention of the development of severe immunosuppression by treating with HAART. HIV-infected children aged <5 years who are CMV infected and severely immunosuppressed (e.g., CD4 count <50 cells/mm^3 or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months **(AIII)**. Older children should be counseled to be aware of "floaters" in the eye and visual changes, similar to the recommendation for adults **(BIII)**. In the HAART era, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents in HIV/CMV-coinfected people is generally not recommended **(CIII)**. CMV end-organ disease is best prevented by using antiretroviral therapy to maintain CD4 count >100 cells/mm^3. If this is not possible, prophylaxis with valganciclovir can be considered for HIV-infected adolescents who are CMV seropositive, have a CD4 count of <50 cells/mm^3, and are large enough to receive adult doses of valganciclovir **(CI)**.

Discontinuing Primary Prophylaxis

Since primary prophylaxis with antiviral agents in HIV/CMV-coinfected people is not recommended (as discussed above) no consideration of discontinuing primary prophylaxis is necessary.

Treatment Recommendations

Treatment of Disease

Treatment of newborns with symptomatic congenital CMV disease involving the CNS with intravenous ganciclovir for 6 weeks has been evaluated in a series of clinical trials conducted by the NIAID Collaborative Antiviral Study Group (CASG) *[600, 601]*; all babies in these studies were HIV uninfected. Babies receiving therapy cleared their urine of CMV by culture by the end of the 6-week treatment period, although all experienced a rebound in their viruria following antiviral discontinuation *[600]*. In a phase III, randomized, controlled trial, babies receiving intravenous ganciclovir for 6 weeks were less likely to have hearing deterioration over the first 2 years of life compared with babies receiving no antiviral therapy *[601]*. Treated babies also had more rapid resolution of liver enzyme abnormalities and a greater degree of growth during the course of therapy. They also experienced fewer neurodevelopmental delays at 1 year of life compared with nontreated subjects *[602]*. However, approximately two-thirds of the infants developed substantial neutropenia during therapy *[601]*. In patients developing neutropenia, 48% required dose modification but most were able to complete the 6 weeks of therapy. Based upon these results, intravenous ganciclovir therapy (6 mg/kg/dose administered every 12 hours) for 6 weeks should be offered to HIV-exposed or HIV-infected babies with symptomatic congenital CMV disease involving the CNS **(BI)**. If during the 6 weeks of therapy a baby is confirmed to be HIV infected, some experts then would recommend a longer duration of treatment (>6 weeks) **(BIII)**.

Management of CMV retinitis should be done in concert with an experienced ophthalmologist. Intravenous ganciclovir, oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis in HIV-infected adults *[603-607]* **(AI)**. For HIV-infected children the drug of choice for initial treatment for CMV retinitis as well as other end-organ disseminated CMV disease (e.g., colitis, esophagitis, and CNS disease) is intravenous ganciclovir **(AI)**. Oral valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis *[605]* **(AI)**. The drug is well absorbed from the GI tract and rapidly metabolized to ganciclovir in the intestine and liver. However, data on appropriate dosage of this drug for children are limited *[608]*. Additionally, a valganciclovir liquid formulation is not commercially available. While extemporaneously compounded valganciclovir "recipes" are available, the pharmacokinetics, bioavailability, safety, and shelf-life of such formulations are unknown and they should not be used in pediatric patients. Thus, oral valganciclovir is an option primarily for older children who are large enough to receive the adult dose and tablet formulation of valganciclovir **(CIII)**.

An alternative drug to treat CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children is foscarnet **(AI)**. Foscarnet employed as suppressive therapy has been associated with increased length of survival relative to ganciclovir in HIV-infected adult patients. Doses should be modified among patients with renal insufficiency.

Combination therapy with ganciclovir and foscarnet delays progression of retinitis in certain patients failing monotherapy *[594, 605, 609, 610]* 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. Combination therapy with intravenous ganciclovir and foscarnet may also be considered in initial therapy of CMV CNS disease **(BII)**. However, combination therapy is associated with substantial rates of adverse effects.

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. Given the lack of commercial availability of oral ganciclovir, its use in children can no longer even be considered.

In adults, the combination of oral valganciclovir with a ganciclovir sustained release intraocular implant, replaced every 6 to 9 months, was superior to daily intravenous ganciclovir in preventing relapse of retinitis and is preferred by some adult HIV specialists for patients with CMV lesions adjacent to the optic nerve or fovea *[603-607]* **(AI)**. This regimen can be considered for treatment and chronic suppression of CMV retinitis in older children who are large enough to receive the adult dose and tablet formulation of valganciclovir.

Cidofovir is effective in treating CMV retinitis among adult patients who are intolerant of other therapies. However, cidofovir has not been studied in pediatric patients with CMV disease **(CIII)**.

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 chamber of the eye also has been used in HIV-infected adults and adolescents. In HIV-infected adults with CMV retinitis, ganciclovir intraocular implant plus oral valganciclovir is superior to once-daily intravenous ganciclovir for preventing relapse of CMV retinitis *[603-605]*. Intraocular implant plus intravenous ganciclovir or oral valganciclovir may be the preferred initial treatment for patients with immediate sight-threatening infections (e.g., adjacent to the optic nerve or fovea). Small peripheral lesions may be treated with systemic therapy without local treatment **(BII)**. Intraocular implants should not be used in children <3 years of age because of the small size of the eyes in young children **(EIII)**. Intraocular cidofovir is not recommended in children because of lack of data and the risk of hypotonia observed in adults.

For CMV neurological disease, initiating therapy promptly is critical for an optimal clinical response. However, concentrations of ganciclovir in the CNS range from 24% – 70% of those in the plasma, with brain concentrations of approximately 38% of plasma levels *[611]*; hence combination treatment with ganciclovir and foscarnet might be preferred as initial therapy to stabilize disease and maximize response **(BII)**. However, this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children receiving optimized HAART is unknown.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Management of CMV retinitis should be done in concert with an experienced ophthalmologist. Recommendations for HIV-infected adults include indirect ophthalmoscopy through a dilated pupil performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, 1 month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment; recommendations should be similar for HIV-infected children with CMV retinitis **(AIII)**. Monthly fundus photographs, using a standardized photographic technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse **(AIII)**. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months. However, because relapse of the retinitis occurs among patients with immune recovery, regular ophthalmologic follow-up still is needed.

The major side effects of ganciclovir and valganciclovir are myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia) and renal toxicity. Dose reduction or interruption due to hematologic toxicity may be necessary in up to 40% of patients receiving intravenous ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate marrow suppression. The main toxicities of foscarnet are decreased renal function and metabolic derangements. Renal toxicity and foscarnet binding to divalent metal ions such as calcium lead 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.

Metabolic disturbances can be minimized if foscarnet is administered by slow infusion, with rates not exceeding 1 mg/kg/minute. Concomitant use of other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscarnet therapy. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter **(AIII)**.

The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction including Fanconi syndrome and acute renal failure. When present, renal toxicity manifests as proteinuria and glycosuria. To minimize nephrotoxicity, probenicid should be administered before each infusion, and intravenous hydration with normal saline should be administered before and after each cidofovir infusion. For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases ≥0.5 mg/dL above baseline.

Immune recovery uveitis is an immunologic reaction to CMV associated with inflammation in the anterior chamber and/or the vitreous in the setting of immune recovery after initiation of effective HAART *[612]*. Ocular complications of uveitis include macular edema and development of epiretinal membranes that can cause loss of vision. Immune recovery uveitis may respond to periocular corticosteroids or a short course of systemic steroids. Oral valganciclovir was beneficial in one small uncontrolled study *[613]*.

Management of Treatment Failure

Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occur despite ganciclovir therapy. Foscarnet is the drug of choice when ganciclovir resistance is suspected **(AI)**.

In patients with CMV retinitis, while drug resistance occurs among patients receiving long-term therapy, early relapse may be due to the limited intraocular penetration of systemically administered drugs; in HIV-infected adults, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment is recommended because it achieves greater drug levels in the eye and often will control the retinitis for 6 to 8 months until the implant requires replacement **(BIII)**. Due to the size requirements of the implants, this option would be limited to older children with CMV retinitis. Many experts would initially treat early first relapse of retinitis with reinduction with the same drug followed by reinstitution of maintenance therapy **(AII)**. However, if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent, change to an alternative drug is reasonable **(AIII)**. Combination ganciclovir and foscarnet can be considered but is accompanied by greater toxicity **(BI)**.

Prevention of Recurrence

CMV disease is not cured with courses of available antiviral agents (e.g., ganciclovir, foscarnet, or cidofovir). After induction therapy, the standard recommendation has been to provide secondary prophylaxis (chronic maintenance therapy) for the remainder of the person's life **(AI)**. Regimens that can be considered for chronic suppression in adults and adolescents include intravenous ganciclovir, oral valganciclovir, intravenous foscarnet, combined intravenous ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration via intraocular implant **(AI)** *[614-621]*. Because of more limited data on drug pharmacokinetics and dosing in children, intravenous ganciclovir or

foscarnet are the preferred secondary prophylaxis regimens for children; oral valganciclovir can be considered for older children able to receive adult dosing. Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir have been reported to be effective for secondary prophylaxis of CMV retinitis *[622, 623]*, although intraocular therapy alone does not provide protection to the contralateral eye or to other organ systems and therefore typically is combined with systemic treatment *[614]*. Additionally, frequent intravitreous injections are impractical for use in most children **(DIII)**.

The choice of a chronic maintenance regimen for patients treated for CMV disease should be made in consultation with a specialist. Chronic maintenance therapy is not routinely recommended for GI disease but should be considered if relapses occur **(BII)**. A role for maintenance therapy for CMV pneumonitis has not been established **(CIII)**. For patients with retinitis, decisions should be made in consultation with an ophthalmologist and should take into consideration the anatomic location of the retinal lesion, vision in the contralateral eye, and the immunologic and virologic status of the patient **(BIII)**. Intraocular implants should not be used in children <3 years of age because of the small size of the eyes in young children **(EIII)**.

Discontinuing Secondary Prophylaxis

Multiple case series have reported that maintenance therapy can be discontinued safely among adult and adolescent patients with CMV retinitis whose CD4 counts have indicated a sustained increase in response to HAART *[624-629]*. These patients have remained disease free for >30 to 95 weeks, whereas during the pre-HAART era, retinitis typically reactivated in <6 to 8 weeks after stopping CMV therapy. Plasma HIV RNA levels were variable among these patients, supporting the hypothesis that CD4 count is the primary determinant of immune recovery to CMV. CMV retinitis can occur in HAART-treated adults with high CD4 counts, however *[630]*, suggesting that CMV-specific cellular immunity may be important in controlling CMV in immune-reconstituted HIV-infected adults *[631, 632]*. In HIV-infected adults with CMV retinitis, discontinuing secondary prophylaxis is considered for patients with a sustained increase in CD4 count to >100 cells/mm^3 in response to treatment.

The safety of discontinuing secondary prophylaxis following immune reconstitution with HAART in HIV-infected children has not been as well studied. Low or undetectable HIV replication in children is the strongest correlate with CMV immune reconstitution, being associated with a higher frequency of CMV-specific CD4 cells *[633]*. Early institution of HAART may assist in controlling CMV infection through maintenance of normal CD4 count and cytotoxic T-lymphocyte responses in HIV-infected children *[634]*. In deciding whether to discontinue secondary prophylaxis, one also must consider the significant toxicities that can be associated with currently available antiviral drugs active against CMV, including those seen in *in vitro* and animal models.

Recognizing the limitations of the pediatric data but drawing upon the growing experience in adult patients, discontinuing prophylaxis may be considered for pediatric patients aged 1 to 6 years who are receiving HAART therapy and have a sustained (e.g., >6 months) increase in CD4 count to >500 cells/mm^3 or CD4 percentage to >15%, and for children aged >6 years, an increase in CD4 count to >100 cells/mm^3 or CD4 percentage to >15%, as for adults **(CIII)**. Such decisions should be made in close consultation with an ophthalmologist and should take into account such factors as magnitude and duration of CD4 cell increase, anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring **(CIII)**.

All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring at at least 3 to 6 month intervals for early detection of CMV relapse, as well as for immune reconstitution uveitis **(AII)**. CMV viral load or other markers of CMV infection (e.g.,

antigenemia or viral DNA tests) are not well standardized; their role in predicting relapse remains to be defined and they are not recommended for routine monitoring **(DIII)** *[635, 636]*.

Re-Initiating Secondary Prophylaxis

Relapse of CMV retinitis occurs among adult patients whose anti-CMV maintenance therapies have been discontinued and whose CD4 counts have decreased to <50 cells/mm^3 *[622]*; reinstitution of secondary prophylaxis is recommended for HIV-infected adults when CD4 count falls to <100 cells/mm^3. For HIV-infected children in whom secondary prophylaxis has been discontinued due to immune reconstitution, secondary prophylaxis should be reinstituted in children aged 1 to 6 years when the CD4 count has decreased to <500 cells/mm^3 or CD4 percentage to <15%, and for children aged >6 years when CD4 count decreases to <100 cells/mm^3 or CD4 percentage to <15% **(BIII)**.

Hepatitis B Virus

Epidemiology

Chronic hepatitis B infection is defined as persistence of hepatitis B surface antigen (HbsAg) for >6 months. Risk for the development of chronic hepatitis B infection after acute infection is correlated with age at the time of hepatitis B virus (HBV) infection. Among those who become infected with HBV, chronic hepatitis B infection develops in ≤90% of infants, 25% – 50% of children aged 1 to 5 years, and 6% – 10% of older children and adolescents *[637-639]*.

Childhood HBV infection may be acquired parenterally, perinatally, or via sexual transmission. Horizontal transmission of HBV can occur secondary to frequent interpersonal contact of nonintact skin or mucus membranes with blood or body fluids that contain blood (e.g., saliva) or from sharing household objects such as toothbrushes or razors. Universal hepatitis B vaccination of newborns has dramatically lowered chronic HBV infection among children and reduced the rates of HBV-related morbidity and mortality in the United States.

Adolescents are at risk for HBV infection through sexual activity or injection drug use. In a study of HIV-infected adolescents at 43 PACTG centers, 19% had evidence of current or resolved HBV infection; the rate of current or resolved HBV infection in HIV-infected female adolescents was twice the United States population-based rates, and for males, nearly 7 times higher *[640]*. Risk for HIV/HBV coinfection in adolescents is related to substance abuse and sexual activity, particularly among men who have sex with men *[641]*.

Most children who acquire HBV perinatally are immunotolerant to HBV. Although they have high HBV DNA levels, serum transaminase levels are usually normal and minimal necroinflammatory liver disease occurs. Childhood-acquired HBV infection is characterized by lower HBV DNA levels, greater serum transaminase elevation, and increased necroinflammatory liver disease compared with perinatally acquired HBV infection *[642]*.

Based on data from the National Health and Nutrition Examination Survey for 1999 – 2004, 0.51% (95% CI 0.3% – 0.9%) of children aged 6 to 19 years had ever been infected with HBV *[643]*. There are limited data on the prevalence of chronic HBV infection in HIV-infected children in the United States. In a study of 228 HIV-infected children at an inner city hospital, 6 HIV-infected children had chronic HBV infection (2.6%; 95% CI 1.1% – 5.9%) *[644]*. The mean age of HIV/HBV-coinfected children was 17 years, 33% had acquired both HIV and HBV infection via blood transfusion, and 84% were HBV early antigen positive (HBeAg), indicative of infectiousness. Half of the coinfected children had normal serum transaminase levels and half had mild elevations of up to 2-fold above upper limit of normal.

Clinical Manifestations

The majority of acute HBV infections in children are asymptomatic. Prodromal symptoms of lethargy, malaise, fatigue, nausea, and anorexia may occur. Jaundice and right upper quadrant pain may follow and, less commonly, hepatomegaly and splenomegaly. Gianotti-Crosti syndrome (papular acrodermatitis), urticaria, macular rash, or purpuric lesions may be seen in acute HBV infection. Extrahepatic manifestations associated with circulating immune complexes that have been reported in children with HBV infection include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. Most children with chronic HBV infection are asymptomatic. However, rare cases of fulminant hepatic failure have occurred during childhood HBV infection *[645]*.

Most children with chronic HBV infection are asymptomatic. One-quarter of infants and children with chronic HBV will eventually develop cirrhosis or hepatocellular carcinoma (HCC) *[646, 647]*. However, these sequelae usually develop over 2 to 3 decades and rarely occur during childhood *[648]*. The development of HCC correlates with HBV DNA levels and duration of HBV infection, with the highest risk seen in those infected in early life *[649]*. HIV/HBV-coinfected adults are at increased risk of cirrhosis, end-stage liver disease, and liver-related mortality *[650]*.

Diagnosis

Testing for HBV infection should be performed in any child whose mother is known to be infected with HBV. Adolescents and young adults who have a history of injection drug use or high-risk sexual contact should also undergo testing for HBV infection.

HBsAg is the first marker detectable in serum, appearing 30 days after infection; it precedes the elevation of serum aminotransferase levels and the onset of symptoms. Necroinflammatory liver disease may then occur, during which time increasing serum transaminase levels are seen, along with high HBV DNA levels and HBeAg positivity. HBeAg correlates with viral replication, DNA polymerase activity, infectivity, and increased severity of liver disease. Antibody to hepatitis B core antigen (anti-HBc) appears 2 weeks after HBsAg and persists for life. Passively transferred maternal anti-HBc can be detectable in the infant up to age 12 months. In self-limited infections, HBsAg is usually eliminated in 1 to 2 months, and hepatitis B surface antibody (anti-HBs) develops during convalescence. Anti-HBs indicates immunity from HBV infection. After recovery from natural infection, both anti-HBs and anti-HBc are usually present. In persons who become chronically infected (i.e., persistently positive for HBsAg beyond 24 weeks), anti-HBs is not detectable. Persons who have been vaccinated may have detectable anti-HBs but not anti-HBc.

HBeAg seroconversion, defined as the loss of HBeAg followed by the production of antibodies to HBeAg (e.g., anti-HBe), heralds the transition of the HBV-infected individual to the inactive carrier state. HBeAg seroconversion is infrequent in children aged <3 years and may not occur until the third or fourth decade of HBV infection *[651]*. Fewer than 10% of children infected perinatally with HBV undergo HBeAg seroconversion. In contrast, higher rates of HBeAg seroconversion occur in childhood-acquired HBV infection, with 70% – 80% of children acquiring anti-HBe by the second decade of life *[648]*. HBeAg seroconversion is usually followed by reduction of serum HBV DNA levels and an initial increase and then subsequent normalization of serum transaminase levels, followed by resolution of necroinflammatory liver disease *[648]*. Development of cirrhosis and HCC occurs more commonly in patients with delayed HBeAg seroconversion *[652]*. HBeAg-negative infection (precore mutant) occurs uncommonly in children *[639]*.

HBV DNA is a marker of HBV replication. In the active phase of chronic hepatitis B, high HBV DNA levels have been associated with necroinflammatory liver disease. Children who were infected perinatally, however, may remain in an immunotolerant phase with high levels of HBV DNA without evidence of liver damage. Quantitative DNA assays may be helpful in determining the need for treatment as well as for evaluating treatment response. Although not necessary for diagnostic purposes, liver biopsy may be useful to assess the degree of liver damage and determine the need for treatment.

Prevention Recommendations

Prevention of Exposure

All pregnant women, including HIV-infected women, should be tested for HBsAg during an early prenatal visit in each pregnancy **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk for HBV infection (e.g., injection drug users, those with intercurrent sexually

transmitted infections, and those with multiple sexual partners). Pregnancy is not a contraindication to hepatitis B vaccination for women who have not been previously vaccinated; current hepatitis B vaccines contain noninfectious HBsAg and should cause no risk to the fetus.

Preventing First Episode of Disease

All infants born to HBV-infected women, including HIV-coinfected women, should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth, a second dose of hepatitis B vaccine at age 1 to 2 months, and a third dose at age 6 months *[39]* **(AI)** (Figures 1 and 2). For preterm infants weighing <2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches age 1 month *[39]*. A three-dose hepatitis B vaccine regimen is 95% effective in preventing HBV infection in HBV-exposed infants. Post-vaccination testing for anti-HBs and HBsAg should be performed at age 9 to 18 months among infants born to HBsAg-positive women. The level of anti-HBs that is considered to be protective is >10 mIU/mL. Infants who are HBsAg negative and have anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose series of hepatitis B vaccine and retested 1 to 2 months after the final dose of vaccine *[39]*.

The three-dose series of hepatitis B vaccine is also recommended for all children and adolescents aged <19 years who were not previously vaccinated, including HIV-infected children. However, diminished antibody responses to hepatitis B vaccination may be seen in HIV-infected children, especially in older children or those with CD4 counts <200 cells/mm^3 *[653, 654]*. For this reason, HIV-infected infants, children, and adolescents should be tested for anti-HBs 1 to 2 months after completing the vaccination series, and if anti-HBs levels are <10 mIU/mL, revaccinated with a second three-dose series of hepatitis B vaccine. Modified hepatitis B vaccine dosing regimens, including a doubling of the standard antigen dose, might increase response rates. However, although a current randomized trial is evaluating the use of various hepatitis B vaccine preparations and doses in HIV-infected youth, no data are available at this time.

The need for booster doses of hepatitis B vaccine in HIV-infected persons has not been determined. Annual anti-HBs testing and booster doses when the anti-HBs levels decline to <10 mIU/mL should be considered in persons with ongoing risk of hepatitis B exposure *[39]*.

All children, including HIV-infected children and those with HBV coinfection, should receive hepatitis A vaccination at age 1 year (i.e., 12 to 23 months), with the two doses in the series administered ≥6 months apart *[40]*. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits (Figures 1 and 2).

HBV-infected children should be advised not to share toothbrushes or other personal care articles that might be contaminated with blood. Although efficiency of sexual transmission of HBV is relatively low, safe-sex practices should be encouraged for all HIV-infected adolescents and young adults; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens including HBV.

Treatment Recommendations

Treatment of Disease

General issues

Individualization of therapy is essential for any HBV-infected child and should be based upon the child's age, age at acquisition of infection, HBV DNA levels, and serum transaminase levels. Antiviral therapy

regimens for chronic hepatitis B are currently approved only for children >2 years of age with compensated liver disease.

Children infected with HBV who are not receiving anti-HBV therapy should be closely monitored with determination of serum aminotransferase levels every 6 months. If persistent elevation of serum transaminase levels is seen (more than 2-fold the upper limit of normal for ≥6 months), HBeAg, anti-HBe, and HBV DNA levels should be obtained. Monitoring of serum transaminases and HBV DNA levels over time is important before the initiation of antiviral therapy to identify patients who may be in the process of spontaneous HBeAg seroconversion who would not require treatment. Liver biopsy is not required prior to treatment but may be helpful in determining the severity of hepatic inflammation and fibrosis and to exclude other causes of liver disease.

There are no clear-cut recommendations for the treatment of chronic childhood HBV infection. HBV-infected children often have milder disease than adults and may show spontaneous HBeAg seroconversion. There are few large randomized controlled trials of antiviral therapies for chronic hepatitis B infection in childhood. Moreover, the long-term safety of many of the agents used in the treatment of chronic hepatitis B infection in adults is not known in children. However, a 2004 consensus meeting of pediatric liver experts recommended that antiviral treatment be considered in children with chronic HBV infection who have necroinflammatory liver disease for >6 months duration *[655]*.

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 HBV viral replication, as indicated by the presence of detectable serum HBV DNA, with or without HBeAg positivity, for >6 months; and (2) persistent elevation of serum transaminase levels (at least twice the upper limit of normal for >6 months); or (3) evidence of chronic hepatitis on liver biopsy **(BII)** *[655]*. Children without necroinflammatory liver disease usually do not warrant antiviral therapy **(DIII)**. Treatment is not currently recommended for children with immunotolerant chronic HBV infection (i.e., normal serum transaminase levels despite detectable HBV DNA) **(DIII)**. The goals of treatment in children with chronic hepatitis B infection are identical to those in adults and include suppression of HBV replication, normalization of serum transaminase levels, acceleration of HBeAg seroconversion, preservation of liver architecture, and prevention of long-term sequelae such as cirrhosis and HCC.

At the present time, the optimal agent and duration of therapy of childhood hepatitis B infection remain unclear. Treatment of chronic hepatitis B infection is evolving; consultation with providers with expertise in treating chronic hepatitis B infection in children is recommended.

Treatment of Chronic Hepatitis B Infection in Adults and Adolescents

To date, six medications have been approved for treatment of chronic hepatitis B infection in adults. These include interferons (both standard and pegylated), nucleoside analogues such as lamivudine, telbivudine, entecavir, and the nucleotide analogue adefovir. FDA-approved HIV antiretroviral medications, such as tenofovir and emtricitabine, also have significant activity against HBV, although they are not approved for this indication. Preferred initial therapies for adults with chronic hepatitis B without HIV infection include pegylated interferon-alfa, entecavir, or adefovir monotherapy. In adults with chronic hepatitis B infection with or without HIV infection, treatment for hepatitis B is considered in HBeAg-positive individuals with HBV DNA ≥20,000 IU/mL (>10^5 copies/mL), HBeAg-negative persons with HBV DNA ≥2,000 IU/mL (>10^4 copies/mL), patients with persistent serum transaminase elevation, or patients undergoing liver biopsy with evidence of cirrhosis or fibrosis *[650]*.

Treatment options for HBV in the setting of HIV infection must take into account the goals of therapy and the impact treatment may have on both HIV and HBV replication. In coinfected patients who require

treatment for chronic hepatitis B, HIV, or both infections, many experts would initiate a fully suppressive regimen for treatment of HIV infection that includes a dual nucleoside analogue backbone with drugs that have dual activity against both HIV and HBV plus a third agent with activity against HIV; this approach may reduce the risk of IRIS, particularly in patients with advanced immune deficiency. Tenofovir plus lamivudine or emtricitabine would be the first-choice option for the nucleoside backbone; the combination of tenofovir with lamivudine was demonstrated to be more effective in suppressing HBV than either drug alone and prevents development of lamivudine resistance *[656]*. In the instances where HIV treatment is not an option but treatment of hepatitis B infection is needed, pegylated interferon-alfa may be used alone as it does not lead to the development of drug-resistant HIV or HBV mutants. The use of tenofovir, lamivudine, or emtricitabine without a fully suppressive HAART regimen should be avoided because of the rapid development of drug-resistant HIV mutations.

Treatment of Chronic Hepatitis B Infection in Children without HIV Infection

Only two drugs (monotherapy with interferon-alfa [standard] or lamivudine) are currently FDA approved for treatment of chronic hepatitis B in children **(AI)**. Pediatric trials of these agents are limited but show that although these medications are well tolerated by children, response rates are low and HBV infection is not fully eradicated by treatment *[657, 658]*. In HIV-uninfected children, HBeAg seroconversion rates after 1 year of treatment are similar *[639]*. Interferon-alfa treatment is given for only 6 months, but requires subcutaneous administration and has more frequent side effects including growth impairment. Although lamivudine is administered orally and has a lower rate of side effects, it requires a longer duration of therapy and has a high rate of resistance if taken for an extended period of time *[639]*.

Although various combination regimens involving sequential or concurrent lamivudine and standard or pegylated interferon-alfa have been studied in children or adults with chronic hepatitis B, the superiority of combination therapy over monotherapy with standard or pegylated interferon-alfa or lamivudine has not been demonstrated, although lamivudine resistance rates may be lower *[659-668]*. A recent study of children with immunotolerant HBV infection suggested possible benefit from sequential lamivudine and interferon-alfa therapy, with 78% of patients clearing HBV DNA by the end of treatment *[662]*. However, at this time, combination therapy cannot be recommended for pediatric HBV infection until more data are available **(DII)**.

Treatment of HIV/HBV-Coinfected Children

None of the clinical studies of treatment of chronic hepatitis B infection have specifically studied children with HIV/HBV coinfection. As in coinfected adults, choice of antiviral therapy for the HIV/HBV-coinfected child involves consideration of whether concurrent HIV treatment is warranted.

- If treatment of chronic hepatitis B but not HIV infection is indicated, standard interferon-alfa would be the preferred agent **(BIII)**. Adefovir could also be considered in older children able to receive adult dosing **(BIII)**. Antiviral drugs with activity against HIV (e.g., lamivudine, emtricitabine, tenofovir, and possibly entecavir) should be avoided to prevent the future development of drug-resistant HIV mutations.
- If treatment of HIV infection but not chronic hepatitis B is indicated, use of a HAART regimen that avoids the use of drugs with activity against HBV (e.g., lamivudine, emtricitabine, or tenofovir) is recommended to prevent the future development of HBV drug resistance **(BIII)**. Alternatively, in older coinfected children who can receive tenofovir, use of a HAART regimen with a nucleoside analogue backbone that contains two drugs effective against HBV (tenofovir plus lamivudine or emtricitabine) can be considered **(BIII)**.
- If treatment of both HIV and chronic hepatitis B is indicated and the child is naïve to lamivudine, an antiretroviral regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**. A regimen containing tenofovir and a nucleoside analogue (either lamivudine or emtricitabine) is preferred for

HIV/HBV-coinfected adults and should be considered for use in older HIV-infected children or adolescents who can receive adult dosage. However, tenofovir is not approved for use in HIV-infected children <18 years and there is no pediatric formulation currently available. While pediatric studies with an investigational pediatric formulation of tenofovir are under way, data are not yet available.

- If treatment for HIV and chronic hepatitis B is indicated and the child is receiving antiretroviral therapy including lamivudine or emtricitabine with HIV suppression but detectable plasma HBV DNA, HBV lamivudine resistance can be assumed. However, HBV drug-resistant isolates may have lower replicative capacity and although controversial, some experts recommend continued use of lamivudine or emtricitabine **(CIII)**. Treatment options for such children who require HBV therapy include the addition of interferon therapy to the antiretroviral regimen **(BIII)**, or tenofovir **(BIII)**, or adefovir if the child can receive adult dosing **(BIII)**. There are insufficient data on other anti-HBV drugs in children to make recommendations.

Interferons

Standard interferon-alfa-2a or -2b is the therapy that has received the most study in children with chronic hepatitis B (without HIV infection) and is recommended for the treatment of chronic hepatitis B infection with compensated liver disease in children without HIV infection aged ≥2 years who warrant treatment **(BII)**. In a review of 6 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 transaminase levels in 39% at treatment completion *[669]*. Six to eighteen months after therapy discontinuation, 29% of children had persistent HBV DNA and 23% demonstrated HBeAg clearance. Children most likely to respond to interferon treatment are of younger age, higher baseline serum transaminase levels, and lower baseline HBV DNA levels *[657, 670-672]*. Response is less likely (10%) in those with normal serum transaminase levels, high HBV DNA levels, HBV genotypes C or D, or those with HBeAg-negative chronic HBV infection. Interferon-alfa therapy might be considered for treatment of chronic hepatitis B in HIV-coinfected children who do not require antiretroviral therapy for treatment of their HIV infection **(BIII)**.

The standard course of interferon-alfa therapy for children without HIV infection is 24 weeks. Pegylated interferon-alfa, which results in more sustained plasma interferon concentrations and can be administered via injection once weekly for 48 weeks, has proven superior to standard interferon-alfa in the treatment of HBV-infected adults *[665, 673]*. However, the limited data on the use of pegylated interferon-alfa in children come from treatment of hepatitis C infection and appropriate dosing information is not available for use of pegylated interferon-alfa for treatment of chronic hepatitis B in children *[674-676]*.

Lamivudine

Lamivudine (3TC) is an oral nucleoside analogue that inhibits HBV replication. It is approved for use in children aged 2 to 17 years with compensated liver disease due to chronic hepatitis B. In a placebo-controlled trial in children with chronic hepatitis B without HIV infection, lamivudine was well tolerated, with virologic response (clearance of HBV DNA and HBeAg) seen in 23% of children receiving 52 weeks of lamivudine therapy, compared with 13% in placebo recipients *[677]*. Response rates were higher (35%) for children with baseline serum transaminases >2 times normal *[677]*. In a 2-year, open-label extension of this study, 213 children who remained HBeAg positive after 1 year of therapy were continued on lamivudine treatment; virologic response was seen in 21% of the original lamivudine recipients, compared with 30% of prior placebo recipients, indicating that additional clinical response could occur over time with prolonged treatment *[678]*. However, longer duration of lamivudine therapy was also associated with progressive development of lamivudine-resistant HBV, with base pair substitutions at the YMDD locus of HBV DNA polymerase. The incidence of YMDD mutations in the prior placebo group increased from 0% at baseline, to 19% at month 12, and 49% at month 24. In the prior lamivudine group, the incidence of YMDD mutations increased from 24% at baseline, to 59% at

month 12, and 64% at month 24 *[678]*. Lower virologic response rates (5%) were seen at 24 months in patients with the YMDD variant, compared with 54% in patients with wild-type virus *[678]*.

Accordingly, lamivudine should not be used as a single agent for treatment of chronic hepatitis B in HIV-infected children because of the risk of developing HIV resistance to lamivudine **(EIII)**; as discussed above, lamivudine should only be used in HIV/HBV-coinfected children in combination with other antiretroviral drugs in a HAART regimen **(BIII)**. It is important to note that the dose of lamivudine required to treat HIV infection is higher than to treat pediatric chronic hepatitis B alone; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfected children to avoid development of lamivudine-resistant HIV **(AIII)**. Lamivudine resistance should be suspected if HBV DNA levels increase during antiviral therapy. Such increases may precede increases in serum transaminase levels (hepatic flare) and liver decompensation *[672]*.

Emtricitabine

Emtricitabine is structurally similar to lamivudine and is active against HBV and HIV, although not approved for treatment of chronic hepatitis B. Like lamivudine, emtricitabine is also associated with a relatively rapid onset of HBV and HIV drug resistance, and patients with suspected lamivudine resistance should be assumed to have cross-resistance to emtricitabine. Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic hepatitis B and not additive. As with lamivudine, emtricitabine should not be used for treatment of chronic hepatitis B in coinfected children who are not being treated with combination antiretroviral therapy for their HIV infection due to the risk of developing HIV-associated resistance mutations **(EIII)**.

Adefovir

Adefovir dipivoxil is an oral nucleotide analogue active against HBV. Adefovir, 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 *[679]*. The development of HBV resistance to adefovir is much lower than with lamivudine, being reported as 2% after 2 years, 4% after 3 years, and 18% after 4 years of therapy in adults *[680]*. These adefovir-associated mutations in HBV *Pol* gene result in only a modest (3- to 8-fold) increase in the 50% inhibitory concentration and are partially cross-resistant with tenofovir. Adefovir is now FDA approved for adults who require treatment for chronic hepatitis B but do not yet require treatment for their HIV infection. Adefovir has been studied in HIV/HBV-coinfected adults with lamivudine-resistant HBV infection and virologic HBV suppression was demonstrated *[679]*. Safety and effectiveness of adefovir for treatment of chronic hepatitis B in children has not yet been established; however, an ongoing randomized clinical trial is evaluating its use in HIV-uninfected children aged 2 to 17 years with chronic hepatitis B *[657]*.

Tenofovir

Tenofovir is a nucleotide analog structurally similar to adefovir that has been shown to reduce HBV DNA levels in adult patients with lamivudine-resistant as well as wild-type HBV infection. Tenofovir is not approved for use in the treatment of chronic hepatitis B. However, a study in HIV/HBV-coinfected adults receiving stable antiretroviral therapy comparing treatment with tenofovir or adefovir found similar efficacy in suppression of HBV DNA without differences in toxicity *[681]*. Another study of HIV/HBV-coinfected adults receiving tenofovir in addition to lamivudine as part of their antiretroviral regimen found that HBV DNA became undetectable in 30% of HBeAg-positive and 82% of HBeAg-negative patients, most of whom had lamivudine-resistant HBV infection *[679]*. As noted earlier, tenofovir is not approved for use in HIV-infected children aged <18 years and there is no pediatric formulation. However, for HIV/HBV-coinfected adolescents who require treatment of both infections and who can receive adult doses, tenofovir in combination with an anti-HBV nucleoside (either lamivudine or emtricitabine) can be

considered for treatment **(BIII)**; a combined formulation of emtricitabine and tenofovir (Truvada) is available for adults. As with lamivudine and emtricitabine, tenofovir should not be used for treatment of chronic hepatitis B in HIV-coinfected patients who are not receiving combination antiretroviral therapy for treatment of their HIV infection due to the risk of developing HIV-associated resistance mutations **(EIII)**.

Entecavir

Entecavir is an oral nucleoside analogue that inhibits HBV DNA polymerase. Compared with lamivudine, entecavir therapy results in greater HBV viral suppression, increased normalization of serum transaminase levels, improved liver histology, and lower HBV resistance rates *[682]*. HBV viral suppression has also been demonstrated in HIV/HBV-coinfected adults. Entecavir treatment is approved for treatment of chronic hepatitis B in adults and is preferred for lamivudine-resistant HBV infections. However, it was recently demonstrated to have suppressive activity against HIV *[683]*. Entecavir should not be used in HIV/HBV-coinfected patients who are not receiving combination antiretroviral therapy for treatment of their HIV infection. There are no pediatric data on safety and efficacy of entecavir.

Telbivudine

Telbivudine is a thymidine nucleoside analogue that was approved for the treatment of chronic hepatitis B in adults. It is well tolerated, but like lamivudine, there is emergence of resistance over time, and telbivudine is not active against lamivudine-resistant HBV. No data are currently available on telbivudine in HIV/HBV-coinfected adults. There are no pediatric data on safety and efficacy of telbivudine.

Duration of Therapy

The optimal duration of therapy in HIV/HBV-coinfected children is not known. The duration of interferon-alfa treatment in HIV-uninfected children with chronic hepatitis B is 6 months. At least 1 year of lamivudine therapy is recommended for HIV-uninfected children with chronic hepatitis B, with continuation of medication for ≥6 months after documented HBeAg seroconversion *[657]*. However, because lamivudine would only be given to HIV/HBV-coinfected children who need HIV treatment and as part of a suppressive antiretroviral regimen, treatment with lamivudine (or other anti-HBV drugs with anti-HIV activity) should be continued indefinitely in children with HIV/HBV coinfection, even in the setting of HBeAg seroconversion **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

The parameters of successful therapy of chronic hepatitis B are not well defined, but markers of improvement would include decreased hepatic necroinflammatory disease, normalization of serum transaminase levels, reduction of HBV DNA levels, and HBeAg seroconversion. In children starting treatment for chronic hepatitis B, serum transaminase levels should be measured every 3 to 6 months. If the child is also initiating HAART, some experts would monitor transaminase levels more frequently in the first few months of therapy (e.g., monthly for 3 months) due to the risk of IRIS (see below). Monitoring of response to treatment for chronic hepatitis B is based on testing for HBV DNA and HBeAg and anti-HBe antibody on the same schedule as transaminase evaluations (every 3 to 6 months). Among persons who are HBeAg positive, treatment for chronic hepatitis B should be continued until HBeAg seroconversion has been achieved and ≥6 months of additional treatment has been completed after the appearance of anti-HBe. Close monitoring for relapse is needed after withdrawal of therapy. Among persons who are HBeAg negative, treatment should be continued until HBsAg clearance has been achieved.

In HIV/HBV-coinfected persons starting HAART, serum transaminase elevations ("flares") may be seen as part of IRIS, or they may occur secondary to HAART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune mediated, and restoration of immunocompetence with antiretroviral treatment may reactivate liver inflammation and damage. Initiation of HAART without anti-HBV therapy may lead to reactivation of HBV. This does not represent a failure of HAART therapy but rather a sign of immune reconstitution. IRIS is manifested by an increase in serum transaminase levels as the CD4 count increases during the first 6 to 12 weeks of HAART. Thus, serum transaminase levels should be monitored closely following introduction of HAART. In such situtations, HAART should be continued and treatment for HBV initiated. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to HAART in terms of immune reconstitution and, perhaps, improved survival. It may be difficult in a patient experiencing a hepatic flare to differentiate between IRIS and drug-induced liver toxicity, and there is no reliable clinical or laboratory predictor to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease is recommended in such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

Clinical and laboratory exacerbations of hepatitis and hepatic flare may occur in children receiving HAART should agents with anti-HBV activity be discontinued. Some experts recommend that once antiretroviral drugs with anti-HBV activity are begun, they 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 discontinuation of therapy for chronic hepatitis B results in a hepatic flare, therapy for chronic hepatitis B should be reinstituted **(BIII)**.

Some clinicians recommend monitoring HBV-infected children or adolescents for HCC development with baseline screening and then yearly determinations of serum alpha fetoprotein (AFP) levels and abdominal ultrasonography, although there are no data to supporting the benefit of such surveillance *[639, 655, 657, 658]*.

Although adverse effects of interferon-alfa use in children, while frequent, are usually not severe or permanent, approximately 5% of children require treatment discontinuation. The most common side effects include an influenza-like syndrome, cytopenias, and neuropsychiatric effects. Influenza-like symptoms consisting of fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, and vomiting are seen in 80% of patients during the first month of treatment. The incidence of these side effects decreases substantially during the first 4 months of therapy; premedication with acetaminophen or ibuprofen might reduce the incidence of side effects. Subtle personality changes have been reported in 42% of children that resolve when therapy is discontinued *[684]*. Depression and suicidal ideation have also been reported in clinical trials of children treated with interferon-alfa *[685]*. Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypo- or hyperthyroidism) have been reported with interferon-alfa therapy *[686]*. Loss of appetite with transient weight loss and impairment in height growth may occur, but usually resolves after completion of therapy *[687]*. Less commonly observed side effects of interferon-alfa include epistaxis and transient mild alopecia. The presence of antinuclear autoantibodies has been detected in some children treated with interferon-alfa. Interferon-alfa therapy is contraindicated for children with decompensated liver disease; severe cytopenias; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease *[688]* **(EII)**. Elevation of serum transaminase levels has been reported during interferon-alfa therapy in children and adults but is not generally an indication to stop therapy; these flares may herald impending HBeAg seroconversion *[657]*. Children receiving interferon-alfa therapy should be monitored with a complete blood count and serum TSH level at baseline and periodically (e.g., at least every 3 months) for the duration of treatment.

Lamivudine is generally well tolerated in children; rare cases of lactic acidosis and pancreatitis have been reported in HIV/HBV-coinfected adults. Tenofovir and adefovir can cause renal tubular disease. Patients receiving either drug should have baseline urinalysis and periodic serum creatinine and phosphate monitoring. Administration of other nephrotoxic agents increases the risk of renal toxicity.

Management of Treatment Failure

Treatment failure is defined as the presence of ongoing HBV replication, persistent serum transaminase elevations, and the failure of HBeAg seroconversion in those who are HBeAg positive. Flares of liver disease with increasing HBV DNA levels can be seen with the development of resistance to lamivudine or emtricitabine.

For children who have received initial treatment for chronic hepatitis B with standard dose interferon-alfa monotherapy, use of higher dose interferon-alfa for retreatment has been found to result in improved response in some children **(CII)** *[663, 689, 690]*. Lamivudine has also been used as secondary therapy for children without HIV infection who have not responded to standard interferon-alfa therapy **(CII)** *[691-693]*; in HIV-infected children, initiation of a lamivudine-based HAART regimen could be considered **(CIII)**.

For HIV/HBV-coinfected children developing lamivudine resistance during therapy, treatment options are more limited because of the lack of pediatric data on adefovir, entecavir, and tenofovir. Because these HBV drug-resistant isolates may have lower replicative capacity than wild-type HBV, some experts recommend continuation of lamivudine or emtricitabine therapy in such cases. Alternatively, the addition of interferon-alfa therapy could be considered or, in children old enough to receive adult doses of tenofovir or adefovir, addition of tenofovir or adefovir to the regimen could be considered **(CIII)**.

Prevention of Recurrence

Not applicable.

Discontinuing Secondary Prophylaxis

Not applicable.

Hepatitis C Virus

Epidemiology

The prevalence of hepatitis C virus (HCV) infection is 0.2% among children aged 1 to 11 years and 0.4% for adolescents aged 12 to 19 years in the United States *[694, 695]*. The prevalence of HCV infection among HIV-infected children may be higher. In a serostudy of 535 HIV-infected children followed at pediatric HIV clinical trial sites, the prevalence of HCV infection by HCV antibody and RNA testing was 1.5% *[696]*. In a more recent study of 228 HIV-infected children at an inner city hospital in the Bronx, 7 HIV-infected children had chronic HCV infection (3.1%; 95% CI 1.4% – 6.5%), defined as a reactive HCV antibody and positive HCV RT-PCR *[644]*. The mean age of HIV/HCV-coinfected children was 16 years and 57% had mild elevation (up to 2-fold above upper limit of normal) in serum transaminase levels.

Mother-to-child transmission is the predominant mode of HCV acquisition in children *[697, 698]*. Other potential sources of HCV infection in older children include injection drug use, body piercing, tattoos, accidental needlestick injury, household contact, and sexual exposure *[699, 700]*. Prior to 1992, blood transfusion was a source of HCV infection in children; a recent look-back study found that 3% of persons who had received blood transfusions in a neonatal intensive care unit between 1975 and 1992 were anti-HCV antibody positive *[701]*. However, the incidence of HCV infection from transfusion has dramatically declined since 1992, when second-generation HCV EIA screening was implemented. With the current additional use of nucleic acid amplification testing, the risk of HCV infection via transfusion is approximately 1 per 2 million *[702]*.

The overall risk for mother-to-infant transmission of HCV from a woman infected with HCV alone ranges from 4% to 10% *[697, 703-710]*. The primary risk factor for perinatal HCV transmission is maternal HCV viremia at delivery, although an absolute threshold for HCV transmission has not been identified *[704, 711-715]*. Available data do not indicate that HCV genotype is related to the risk for perinatal HCV transmission *[704, 710]*. Although a few studies have suggested that vaginal delivery increases the risk of HCV transmission *[703, 705, 707, 711]* and that HCV can be transmitted during the intrapartum period *[716]*, most studies have found that mode of delivery does not appear to influence perinatal HCV transmission *[698, 705, 706, 708, 717-720]*. Additionally, while HCV can be detected in breast milk *[721]*, studies of infants born to HCV-infected women have not demonstrated an increased risk for HCV transmission in infants who are breastfed compared with those who were formula fed *[698, 703-706, 708, 714, 716, 717, 721]*.

Maternal HIV coinfection increases the risk of perinatal HCV transmission, with perinatal HCV transmission rates of 6% – 23% reported for infants born to women coinfected with HCV and HIV *[697, 703-705, 709, 715, 718-720, 722-727]*. Furthermore, a few studies suggest that children who acquire perinatal HIV infection may be more likely to acquire HCV infection from HIV/HCV-coinfected mothers than children who did not acquire HIV *[718, 719, 725, 727]*. Reported dual-virus transmission has been reported in 4% – 10% of children born to HIV/HCV-coinfected mothers *[703, 718, 723, 725, 726]*. It is hypothesized that HCV RNA levels may be higher among women coinfected with HIV than women infected with HCV alone, which could in part account for the increased risk for mother-to-child HCV transmission from HIV/HCV-coinfected women, although not all studies have found higher levels of HCV viremia among HIV-infected mothers *[713, 719, 722]*. One European study has suggested that HCV perinatal transmission may be reduced among HIV-infected women receiving HAART *[720]*.

Chronic HCV infection, defined as the presence of HCV RNA for >6 months, appears to spontaneously resolve in 15% – 40% of adults *[728]*. Findings from a limited number of longitudinal studies of children with perinatal HCV infection suggest that 17% – 59% have spontaneous resolution of HCV infection

[729-734]. Viral clearance occurs by age 3 years in most children and may be more frequent in children infected with HCV genotype 3 *[733, 735]*.

Clinical Manifestations

Children with perinatal HCV infection appear to have a more benign clinical course than adults with newly acquired HCV infection *[699, 736, 737]*. Most HCV-infected children are asymptomatic, with minor abnormalities such as hepatomegaly or mild nonspecific symptoms such as fatigue, myalgias, and poor weight gain *[699, 737, 738]*; however, intermittent asymptomatic elevations in transaminase levels in the first 2 years of life are common *[732, 738, 739]*. In a large European cohort of HCV-infected children, about 20% of children had apparent clearance of HCV viremia; 50% had chronic asymptomatic infection, characterized by intermittent viremia, rare hepatomegaly, and usually normal liver transaminase levels; and 30% had chronic active infection with persistent viremia and abnormal transaminase levels *[733]*.

Histopathologic inflammatory changes of chronic hepatitis may be present in persons with chronic HCV infection despite lack of symptoms, normal serum transaminase levels, and low HCV RNA levels *[738]*. However, most children with chronic HCV infection that have undergone liver biopsy and are included in published studies typically have mild-to-moderate liver disease as determined by signs of structural alterations, inflammatory activity, and necrosis *[699, 713, 737, 739]*. A small subset of children may develop more severe liver disease. In a study of 60 children with perinatally or transfusion-acquired HCV infection who were infected for a mean duration of 13 years, 12% of patients were found to have significant fibrosis on liver biopsy *[737]*. Older age at time of infection and elevated serum gamma-glutamyltranspeptidase correlated with fibrosis; serum transaminase levels correlated with inflammation *[737]*.

In HIV/HCV-coinfected adults, the natural history of HCV infection appears to be accelerated, with more rapid progression to cirrhosis, decompensated liver disease, HCC, and death *[740, 741]*. There are minimal data on the effect of HIV/HCV coinfection on the natural history of HCV infection in children and there are insufficient data to draw conclusions about HCV disease progression in coinfected children *[697]*.

Data on the impact of HCV infection on HIV disease progression in adults are conflicting, with some studies suggesting higher rates of HIV progression and others not observing this *[697]*. The effect of pediatric coinfection on HIV disease progression is also unclear, as the number of coinfected children is small and few studies have evaluated this. Two studies of children with perinatal HIV/HCV coinfection did not observe an increase in HIV progression, but a study of older HIV/HCV-coinfected children with thalassemia infected via transfusion did observe more rapid disease progression and increased mortality compared to children infected only with HIV *[718, 726, 742]*.

Diagnosis

Testing for HCV infection should be considered in any child whose mother is known to have HCV infection. It is recommended that all HIV-infected adults or adolescents be tested for HCV infection.

Serologic and nucleic acid tests (NAT) are used to diagnose HCV infection. HCV RNA first becomes detectable 1 to 3 weeks following HCV infection and precedes serologic response to HCV *[728]*. Currently, a third-generation EIA is available for detection of antibody to HCV (anti-HCV). Passively transferred anti-HCV maternal antibodies may be detected among infants born to HCV-infected mothers for up to 18 months. In a large cohort of HCV-exposed but uninfected children, anti-HCV antibodies were present in 15% of children at 12 months, 5% at 15 months, and 2% at 18 months *[713]*. Therefore, only the presence of persistent HCV viremia can be used to reliably verify HCV infection in at-risk infants

aged <18 months *[743]*. HCV infection can be diagnosed in such infants using a NAT for the detection of HCV RNA after 1 month of age; the sensitivity of the HCV RNA testing is low at birth (22%) but increases to 85% at 6 months *[744]*. The majority of children with perinatal HCV infection will have a positive HCV RNA test by age 12 months. However, because of intermittent viremia, a single negative HCV RNA test is not conclusive evidence of infection, and HCV RNA should be tested on at least two occasions between the ages of 2 and 6 months to definitively exclude a diagnosis of HCV infection in an HCV-exposed infant *[744]*.

A positive anti-HCV antibody test in a child aged >18 months is indicative of HCV infection. Supplemental testing with a more specific assay, such as HCV RNA testing, is recommended to prevent the reporting of a false-positive result. A positive HCV RNA test confirms the presence of HCV infection, and, if positive for >6 months, suggests the presence of chronic infection. HCV RNA can be measured qualitatively or quantitatively. Qualitative NATs include qualitative PCR and transcription-mediated amplification. Quantitative tests include branched-chain DNA amplification, quantitative PCR, and real-time PCR and are most useful for monitoring response to anti-HCV therapy *[728]*. Quantitative HCV RNA level (i.e., HCV viral load) does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important information about the response to antiviral therapy. Substantial variability exists among available assays, and if serial values are required to monitor antiviral therapy, continued use of the same quantitative assay for all assessments is strongly recommended.

Liver biopsy is currently the most accurate test to assess the severity of hepatic disease and quantitate the amount of hepatic fibrosis present. A liver biopsy may be useful for determining whether to initiate therapy for chronic HCV infection *[655, 745]*. However, liver biopsy is not required prior to the initiation of anti-HCV therapy, particularly in patients with a high probability of responding to therapy.

There are more than 6 HCV genotypes, with genotype 1 occurring most commonly in the United States *[728]*. Persons with HCV genotypes 2 and 3 are more likely than those with genotype 1 to achieve a sustained virologic response to anti-HCV therapy and thus, results from a liver biopsy may be less likely to affect the decision about the need for treatment in patients with genotypes 2 or 3 *[655, 685]*.

Prevention Recommendations

Prevention of Exposure

All HIV-infected individuals, including HIV-infected pregnant women, should be screened for HCV. There is currently no reliable strategy to prevent perinatal HCV transmission. Cesarean delivery is not associated with reduced perinatal transmission of HCV infection and is not recommended for this purpose for women with chronic HCV infection who are HIV uninfected. Scheduled cesarean delivery is recommended for HIV-infected women with HIV RNA levels >1,000 copies/mL near the time of delivery to prevent perinatal HIV transmission. The limited data available suggest that breastfeeding does not transmit HCV. However, to prevent HIV transmission in the United States, where safe infant formula is available, it is recommended that HIV-infected women should not breastfeed *[746]*.

There are currently no vaccines available to prevent HCV infection.

Adolescents considering tattooing or body-piercing should be informed of potential risks for acquiring HCV, which could be transmitted if equipment is not sterile or if proper infection control procedures are not followed, and to avoid injection drug use and unprotected sex *[747]*. HCV-infected persons should be advised not to share toothbrushes, razors, and other personal care articles that might be contaminated with blood to prevent transmission of HCV to others.

Preventing First Episode of Disease

Patients with chronic liver disease can develop fulminant hepatitis from hepatitis A or B infection; all children (regardless of HIV and HCV infection status) should receive standard immunization with hepatitis A and B vaccines **(AIII)** *[39, 40, 747]*.

Treatment Recommendations

Treatment of Disease

There are a limited number of published studies on treatment of HCV-infected children from which to make treatment recommendations. Pediatric trials that are currently under way in the United States, including the PEDS-C study, a randomized, double-blind, placebo-controlled trial of pegylated interferon-alfa with and without ribavirin, should provide additional data in the future. Data on treatment of children coinfected with HCV and HIV are even more limited. Consultation with providers with expertise in treating chronic pediatric HCV infection is recommended.

HIV/HCV-Coinfected Adults and Adolescents

Current guidelines suggest that treatment be considered in any nonpregnant HCV-infected adult with abnormal serum transaminase levels with a liver biopsy showing chronic hepatitis with significant fibrosis and compenstated liver disease *[748]*. Treatment should be considered for those for whom potential benefits of treatment are judged to outweigh potential risks, including those infected with HCV genotype 2 or 3, those with stable HIV infection not requiring antiretroviral therapy, and those with cryoglobulinemic vasculitis or glomerulonephritis *[745, 749]*. Baseline serum HCV RNA level and HCV genotype are the primary predictors of response to treatment; younger age, higher CD4 count, elevated transaminase levels, lack of liver fibrosis, low body mass index, lack of insulin resistance, and white race are some other variables associated with better treatment response *[749]*. The recommended treatment is combined pegylated-interferon-alfa-2a or-2b plus daily oral ribavirin for 48 weeks regardless of HCV genotype. In HIV/HCV-coinfected adults, sustained virologic response (SVR) rates range from 44% to 73% for treatment of HCV genotype 2 and 3 infection, and 14% – 29% for HCV genotype 1 infection *[639, 750, 751]*. Although some data from clinical treatment trials reported at recent conferences suggest better SVR rates, these may be due to better preselection of patients for therapy or improved adherence following dose adjustment(s). Improved response to anti-HCV treatment is seen in HIV-infected adults with CD4 count >200 cells/mm^3, and therefore HAART should be considered prior to the initiation of anti-HCV therapy in HIV-infected patients with CD4 count <200 cells/mm^3. Anti-HCV treatment is not generally recommended during pregnancy for HCV-infected women because ribavirin is teratogenic.

HCV-Infected Children without HIV Infection

Treatment of HIV-uninfected children with HCV infection aged <3 years is generally not recommended as spontaneous HCV clearance may occur in this age group **(DIII)**. All decisions regarding treatment of HCV infection in children should be individualized since HCV generally causes mild disease in children and there are few data to identify risk factors that differentiate those at greater risk of progression of liver disease *[639, 752]*.

The only currently FDA-approved therapy for HCV-infected children between the ages of 3 and 17 years with compensated liver disease is combined standard interferon-alfa-2b and ribavirin. Standard interferon-alfa is given by subcutaneous injection three times per week. Ribavirin oral solution has been approved for treatment of chronic HCV infection among children aged ≥3 years. For HIV-uninfected children with HCV infection, a 24-week course of therapy is recommended for genotypes 2 and 3; 48-week courses are given for other HCV genotypes. Combination therapy with standard interferon-alfa and ribavirin results in overall SVR rates ranging from 46% to 65% and is well tolerated in children *[655, 685, 753-756]*. Similar

to data from adults, children infected with genotype 1 were less likely to have an SVR (36% compared with 84% of those infected with genotype 2 or 3) *[685]*. Other factors associated with favorable response to anti-HCV treatment in children include lower pretreatment HCV RNA levels, white race, and possibly younger age *[655]*.

HIV/HCV-Coinfected Children

There are no specific treatment studies of children with HIV/HCV-coinfection and recommendations are primarily based on adult data. Since therapy for HCV infection is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected individuals, including HIV-infected children age >3 years in whom there are no contraindications to treatment **(BIII)**. Some specialists would treat children infected with HCV genotypes 2 or 3 without first obtaining a liver biopsy. Pegylated interferon-alfa, which is administered via injection once weekly for 48 weeks combined with ribavirin, is recommended for treatment of HCV infection in adults. However, pegylated interferon-alfa is not currently FDA approved for use in HCV-infected children, although it is under study. Based on the increased efficacy of combination therapy with ribavirin and either standard or pegylated interferon-alfa and data from adults, treatment of HCV-infected children, regardless of HIV status, should include combination therapy with ribavirin and interferon-alfa **(BIII)**. In HIV/HCV-coinfected adults, the recommended duration of treatment is 48 weeks for infections with all HCV genotypes, including 2 and 3, because coinfected adults may not respond as well as those without HIV infection and may have greater relapse rates. Moreover, the efficacy of shorter treatment duration has not been adequately evaluated in HIV-infected persons *[749]*. By extrapolation, 48 weeks of therapy are also recommended for HIV/HCV-coinfected children **(BIII)**. The concomitant use of antiretroviral therapy and anti-HCV therapy is complicated by potential drug interactions. Ribavirin enhances phosphorylation of didanosine, which could increase the risk of toxicity; therefore, these drugs should not be used together **(EI)**. Ribavirin and zidovudine both are associated with anemia and when possible should not be administered together **(DII)** *[749]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Although there are no evidence-based long-term monitoring guidelines for children with perinatally acquired HCV, many experts monitor HCV RNA levels and serum transaminase levels every 6 to 12 months and hemogram and serum AFP levels annually *[747]*. Serum transaminase levels can fluctuate and do not necessarily correlate with histologic liver damage, as significant liver disease can be present in patients with normal serum transaminase levels. In HCV-infected persons without HIV, HCC is rarely seen in the absence of cirrhosis. The benefit of serum AFP and abdominal sonography as screening tools for HCC have not been studied in children. Some experts will perform periodic sonographic screening at defined intervals (every 2 to 5 years) in children with chronic HCV infection, whereas other experts will do these tests only in those with advanced liver disease and/or rising serum AFP concentrations *[747]*. The risk for development of HCC in HCV-infected children, with or without HIV infection, is not known.

HCV RNA quantitation is used to monitor response to antiviral therapy. HCV RNA levels should be performed at baseline, after 12 and 24 weeks of antiviral therapy, at the time of treatment completion (48 weeks), and 6 months after treatment cessation. Some experts will continue to perform serial HCV RNA testing at 6- to 12-month intervals for an additional 1 to 5 years to exclude late virologic relapse. Decreases in HCV RNA ≥2 logs below the baseline during the first 12 weeks of therapy constitute an early virologic response (EVR) *[728]*. An SVR is defined as the absence of detectable HCV RNA using an HCV RNA assay with a lower limit of detection of ≥50 IU/mL at 24 weeks after the end of antiviral treatment. Relapse is defined as HCV RNA rebound at the end of therapy following an initial response to undetectable HCV RNA levels. Nonresponse is defined as the failure to suppress HCV RNA below detection at any time during treatment, whereas breakthrough is the re-emergence of detectable HCV RNA following suppression below the limits of detection despite the continuation of therapy.

In the absence of data from HIV/HCV-coinfected children, the same criteria should be used for determining response to therapy as in HIV/HCV-coinfected adults. If an EVR is observed after the first 12 weeks of treatment, completion of additional HCV therapy is recommended. Adult patients who fail to achieve an EVR by week 12 have a limited chance (<3%) of achieving SVR regardless of duration of therapy, and treatment may be discontinued after 12 weeks in such patients. Persons who achieve a ≥2 $\log_{10}$ reduction in HCV RNA level but remain HCV RNA detectable after 12 weeks of therapy should be retested after the completion of 24 weeks of therapy. If HCV RNA remains detectable after 24 weeks, anti-HCV treatment should then be stopped, whereas an additional 24 weeks of therapy is indicated (total 48 weeks) if HCV RNA is not detected at that time. Persons who achieve an undetectable HCV RNA level after 12 weeks of therapy should complete an additional 36 weeks of anti-HCV treatment (total 48 weeks).

In addition to HCV RNA quantitation, patients receiving antiviral therapy for HCV infection should be closely monitored for medication side effects with complete blood count, serum transaminase levels, and tests of thyroid function. If the child is also initiating HAART, some experts would monitor transaminase levels more frequently in the first few months of therapy (e.g., monthly for 3 months) due to the risk of IRIS (see below).

Side effects of interferon-alfa in children, while frequent, are usually not severe; approximately 5% of children require treatment discontinuation. The most common side effects include influenza-like symptoms consisting of fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, and vomiting, seen in 80% of patients during the first month of treatment. However, these symptoms usually resolve over time and are usually not treatment limiting; premedication with acetaminophen or ibuprofen might reduce the incidence of side effects. Subtle personality changes that resolve when therapy is discontinued have been reported in 42% of children *[684]*. Depression and suicidal ideation have also been reported in clinical trials of children treated with interferon-alfa *[685]*. Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypo- or hyperthyroidism) have been reported with interferon-alfa therapy *[686]*. Loss of appetite with transient weight loss and impairment in height growth may occur, but usually resolves after completion of therapy *[687]*. Less commonly observed side effects of interferon-alfa include epistaxis and transient mild alopecia. Certain children have experienced antinuclear autoantibodies. Interferon-alfa therapy is contraindicated for children with decompensated liver disease; substantial cytopenias; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease *[688]* **(EII)**.

Side effects of ribavirin include hemolytic anemia and lymphopenia. Ribavirin-induced hemolytic anemia is dose dependent and usually presents with a substantial decrease in hemoglobin within 1 to 2 weeks of ribavirin initiation, but the trend usually stabilizes. Significant anemia (hemoglobin <10 gm/dL) occurs in only about 10% of ribavirin-treated children *[752]*. Use of erythropoietin for the management of clinically significant anemia during HCV treatment can be considered. Coadministration of didanosine is contraindicated in children receiving ribavirin, since this combination may increase the risk of mitochondrial toxicity and hepatic decompensation. Children receiving concomitant zidovudine may be more likely to experience bone marrow suppression, and if possible, zidovudine should be avoided in children receiving ribavirin. If zidovudine and ribavirin are given together, the child should be closely monitored for neutropenia and anemia. Ribavirin is teratogenic and should not be used in pregnant women. Sexually active female and male adolescents or those likely to become sexually active who are receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy.

As with HIV/HBV coinfection, the institution of HAART therapy in HIV/HCV-coinfected patients may result in worsening hepatitis, with increases in serum transaminase levels and clinical signs of liver disease including hepatomegaly and jaundice. This does not represent a failure of HAART therapy but rather a sign of immune reconstitution. IRIS is manifested by an increase in serum transaminase levels as the CD4 count increases during the first 6 to 12 weeks of HAART. Thus, serum transaminase levels should be monitored closely following introduction of HAART in HIV/HCV-coinfected children. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to HAART in terms of immune reconstitution and, perhaps, improved survival. It may be difficult in a patient experiencing a hepatic flare to differentiate between IRIS and drug-induced liver toxicity, and there is no reliable clinical or laboratory predictor to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease is recommended in such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

Management of Treatment Failure

There are no data on which to base recommendations for treatment of HIV/HCV-coinfected children or adults who fail to respond to initial HCV treatment. In HIV/HCV-coinfected adults, a second course of treatment for nonresponders (those who fail to achieve EVR by week 12 or undetectable HCV load at week 24) or patients who relapse has limited chances of resulting in SVR. Therapeutic interventions for such patients need to be individualized based on the prior response, tolerance, and adherence to therapy; severity of liver disease; viral genotype; and other underlying factors that might influence response. Some experts might extend the duration of treatment (e.g., 72 weeks) in adult patients who experience a virologic response followed by relapse after adequate HCV therapy, or for patients with advanced fibrosis, long-term administration of low-dose pegylated interferon. No data exist in HIV/HCV-coinfected children on which to base a recommendation.

Prevention of Recurrence

Not applicable.

Discontinuing Secondary Prophylaxis

Not applicable.

Human Herpesvirus 6 and 7 (HHV-6 and HHV-7)

Epidemiology

Human herpesvirus 6 (HHV-6) and 7 (HHV-7) are two closely related members of the *Roseolovirus* genus of herpesviruses. Humans are the only known natural host for these two viruses. The cellular reservoir is believed to be peripheral blood mononuclear cells (PBMCs) and possibly epithelial cells of the salivary glands as well as the bronchial tree. The infection is believed to be primarily transmitted through saliva; sexual transmission may occur, and presumptive *in utero* infection has been described as well. Reactivation, with salivary shedding, occurs frequently among immunocompetent children and adults *[757]*.

There are two subtypes of HHV-6, A and B. HHV-6B is the etiologic agent found in most primary infections, while HHV-6A has been linked to neurologic syndromes. The vast majority of children become infected with HHV-6 early in childhood with 70% – 90% of children HHV-6 seropositive by age 2 years; virtually 100% acquire infection by age 3 years *[758, 759]*. In a large prospective study of North American children, the peak age of acquisition of HHV-6 was 6 to 9 months *[765]*. Such infection is associated with varied clinical manifestations, viremia, and the frequent persistence of the viral genome in PBMCs *[760]*.

HHV-6 can also be transmitted from mother to child. In several recent studies, virtually 100% of pregnant women were HHV-6 seropositive. During pregnancy, 2% – 19 % of women shed virus in the genital tract *[761, 762]*. Congenital HHV-6 infection has been documented in ≤2% of newborns *[759, 763-765]*. In one large study of more than 5,000 births, 1% of cord blood samples were positive for HHV-6 DNA. None of the congenitally infected infants were symptomatic *[765]*. It does not appear that the virus is transmitted by breastfeeding.

HHV-6 infects the same target cells as HIV, and both HHV-6 and HIV can simultaneously infect the same CD4 cells under experimental conditions. There is some evidence for interactions between HHV-6 and HIV at the cellular or molecular levels. Some studies have suggested that HHV-6 upregulates HIV expression in coinfected cells *in vitro [766, 767]*.

In a study of HHV-6 infection in 227 children born to HIV-infected mothers, 3 of 41 (7%) HIV-uninfected infants were positive for HHV-6 DNA in the first month of life, suggesting possible intrauterine infection *[758]*. The cumulative infection rates of HHV-6 at 6 and 12 months of age were significantly lower in HIV-infected children (11% and 33%, respectively) than in uninfected children (28% and 78%, respectively), and there was an association between high CD4 percentage (>15%) in the child before HHV-6 infection and high HHV-6 infection rate. However, when comparing longitudinal HIV disease progression in infants who were HIV infected, HIV disease progressed in all 10 infants with HIV/HHV-6 coinfection and in only 58% of those without HHV-6 coinfection, suggesting that HHV-6 coinfection might increase risk of HIV disease progression.

HHV-7 is acquired later in life than HHV-6. In contrast to HHV-6, the seropositivity to HHV-7 is approximately 50% at age 2 years. Reactivation and/or persistent shedding may occur as well. Salivary shedding is quite common, noted in up to 90% of seropositive adults, and viral DNA has been found in breast milk (unlike HHV-6) *[768]*.

Clinical Manifestations

Many cases of primary infection with HHV-6, which usually occurs by age 2, are asymptomatic or accompanied by mild, nonspecific symptoms. The most common symptom associated with primary

infection is fever, which can be high and abrupt, associated with crankiness and rhinitis. In several studies, primary HHV-6 infection was associated with infants seeking care for acute febrile illness. Among infants <3 years of age presenting for evaluation of a febrile illness, 10% were found to have primary HHV-6 infection; the incidence was 20% among febrile infants aged 6 to 8 months *[769]*.

HHV-6 is the causative agent of most cases of exanthem subitum (ES; also known as roseola infantum), a febrile illness of early childhood associated with a distinctive exanthem. The incidence of HHV-6-related ES peaks between 6 and 9 months of age and is associated with fever of 4 to 5 days, with the rash developing as the fever subsides *[770]*. Ten to twenty percent of infants with primary HHV-6 infection will present with ES. HHV-7 has also been associated with cases of ES.

Primary infection, as well as reactivation, with HHV-6 has also been associated with several CNS syndromes in immunocompetent children and adults, including febrile and nonfebrile seizures, encephalitis/encephalopathy, and acute necrotizing encephalopathy *[769, 771, 772]*. Convulsions are a characteristic feature of severe HHV-6 infection, and these convulsions can often be prolonged and complicated *[773]*.

Reactivation of HHV-6 occurs among adults with immunodeficiency or patients on immunosuppressive therapy following transplantation. In more than 50% of transplant recipients, reactivation occurs within 6 weeks following transplantation. Most reactivation involves HHV-6B. Many episodes of reactivation are asymptomatic, but when symptoms occur, they may include fever, skin rash, and leucopenia. Pneumonitis, encephalitis, bone marrow suppression, and graft versus host disease have been associated with reactivation of HHV-6 following bone marrow transplantation *[774, 775]*.

Persons with HIV infection exhibit frequent reactivation of HHV-6 *[774]*; whether this causes symptoms or progression of illness is controversial. The symptoms most likely to be associated with HHV-6 are pneumonitis and encephalitis.

Reactivation of HHV-7 also occurs in immunocompetent and immunodeficient individuals. The relationship of HHV-7 reactivation to disease states is still poorly understood.

Diagnosis

Many primary infections result in a nonspecific febrile illness. For the 10% – 20% of primary infections that manifest as ES, the clinical diagnosis can be made based on the symptomatology and the distinctive rash.

The diagnosis of HHV-6 related illness can be quite difficult due to the frequent reactivation found in immunocompetent healthy children and adults. Specific testing for HHV-6 or -7 infection may be performed using laboratory methods such as serology, culture, antigen detection, PCR, *in situ* hybridization, immunohistochemistry, or other tests. In considering these tests, the latent nature of these herpesviruses must be recognized and it must be understood that tests differ in their ability to distinguish nonreplicating, latent virus from replicating, active virus *[776]*. Laboratory evaluations (e.g., serology and PCR) to diagnose HHV-7 infections are rarely utilized and are typically limited to research purposes.

Demonstration of an HHV-6-specific antibody seroconversion or significant change in antibody titer between acute and convalescent paired sera can diagnose infection with HHV-6; there may be delay between initial infection and seropositivity, especially in immunodeficient patients. Available serology has variable sensitivity and does not distinguish between HHV-6A and HHV-6B. There may be some cross-reactivity with HHV-7.

Identification of HHV-6 or -7 in PBMCs by virus culture firmly establishes the presence of active infection in immunocompetent hosts, but association with specific disease is more problematic in immunocompromised patients due to a low background rate of viremia. Virus culture requires cocultivation with PBMCs or cord blood and requires 1 to 3 weeks *[776]*. Therefore, it is presently available only in specialized research laboratories.

PCR can be used to detect HHV-6 DNA or RNA. A positive serum, plasma, or PBMC viral DNA or RNA PCR assay, in the absence of measurable antibody, indicates a primary infection. As HHV-6 is found in cellular material such as PBMCs and tissue even during latency, after primary infection a positive DNA PCR cannot be used to establish reactivation, whereas detection of cell-free viral DNA or RNA in plasma, serum, or CSF by PCR *[775]* is taken as evidence of active viral replication and therefore reactivation in a seropositive patient. Correlation of evidence of reactivation and clinical disease must be made cautiously due to the frequent asymptomatic reactivation found in most adults and children *[774, 775]*.

Prevention Recommendations

Preventing Exposure

As HHV-6 and HHV-7 infections are ubiquitous, prevention of primary infection is not possible. Among transplant recipients, prophylactic ganciclovir may decrease the number of episodes and severity of HHV-6 reactivation *[777, 778]*.

Preventing First Episode of Disease

Given the ubiquity of HHV-6 and -7 during early childhood and the lack of an effective vaccine, prevention of HHV-6 disease is not feasible.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

The majority of HHV-6 primary infections result in a mild, self-limited, febrile illness. For the immunodeficient adult or child with possible HHV-6-associated lung or CNS disease, care must be used to exclude other diagnostic possibilities. There are no clear indications for treatment of HHV-6 infection in HIV-infected children, although treatment might be considered for the rare instance of severe encephalitis proven to be due to HHV-6. However, there are no clinical trials or proven therapies for HHV-6. Based on data in adults, the drugs that might be considered for severe HHV-6 disease are ganciclovir, foscarnet, and cidofovir. However, although *in vitro* data suggest ganciclovir and foscarnet are active against HHV-6, there are only limited data to support their use among HIV-infected patients with possible HHV-6 related illness **(CIII)** *[775, 779, 780]*. Ganciclovir has been used for treatment of HHV-6 encephalitis in adult transplant patients *[781]*. However, limited success of ganciclovir therapy in preventing fatal outcome has been reported; in the patients who experienced a fatal outcome, ganciclovir did not achieve a reduction of HHV-6 load in CSF *[782]*. Case reports have documented both successful and disappointing results of foscarnet treatment for HHV-6 encephalitis in transplant recipients *[782-784]*. Cidofovir followed by foscarnet has been used in a stem cell transplant recipient who developed HHV-6 encephalitis with evidence of a significant reduction in HHV-6 load in CSF and in plasma after cidofovir administration *[785]*. There has been one case report of successful use of high-dose ganciclovir

to treat HHV-6 encephalitis in a pediatric bone marrow transplant patient *[786]*. Given the lack of data in children, no specific recommendations can be made.

HHV-7 has not been recognized as being responsible for any specific disease in HIV-infected individuals and no treatment is indicated.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

The major side effect of ganciclovir is myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia). Dose reduction or interruption due to hematologic toxicity may be necessary in ≤40% of patients receiving intravenous ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate marrow suppression. The main toxicities of foscarnet are decreased renal function and metabolic derangements. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts, serum electrolytes, and renal function should be performed twice weekly during induction therapy and once weekly thereafter. The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction including Fanconi syndrome and acute renal failure. When present, renal toxicity manifests as proteinuria and glycosuria. To minimize nephrotoxicity, probenicid should be administered before each infusion and intravenous hydration with normal saline should be administered before and after each cidofovir infusion. For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases ≥0.5 mg/dL above baseline.

HHV-6 and -7 have not been shown to be demonstrated to be associated with IRIS with HAART treatment in HIV-infected children or adults.

Management of Treatment Failure

Mutations conferring resistance of HHV-6 to ganciclovir, cidofovir, and foscarnet have been described *[787]*. It is unknown if a change from one drug to the other would be beneficial.

Prevention of Recurrence

No data exist on prevention of HHV-6 or HHV-7 reactivation from latency in HIV-infected patients.

Discontinuing Secondary Prophylaxis

Not applicable.

Human Herpesvirus-8 (HHV-8) Disease

Epidemiology

Human herpesvirus-8 (HHV-8) is a transmissible DNA virus, with similarities in DNA structure to Epstein-Barr virus. HHV-8 has been causally linked to all forms of KS (HIV-related and endemic KS), and two rare neoplastic conditions usually associated with HIV infection, body cavity-based lymphoma and multicentric Castleman's disease. The exact mechanism by which HHV-8 infection leads to neoplastic disease has not been fully elucidated, but in general, seroconversion to HHV-8 antibody positivity virtually always precedes development of the tumors *[788]*. Higher plasma HHV-8 DNA titers are associated with an increased risk of the development of KS *[789]*.

The prevalence of antibodies to HHV-8 varies widely with age and geography. In the United States and Europe, 1% – 3% of the general adult population is seropositive, with higher rates among men who have sex with men (8%) *[790]*. Among other adult men in the general population, HHV-8 seropositivity was marginally associated with duration of heterosexual activity and positively associated with the number of lifetime sexual partners and coinfection with HBV and herpes simplex type 2 viruses, but none of these were significantly associated with risk for women. In contrast, the seropositivity rate in some areas of Africa is >80% *[791-794]*.

HHV-8 is transmitted via oral and genital secretions. Immunocompetent HHV-8-infected adults frequently shed HHV-8 in their oropharyngeal secretions, with virus detected in saliva on 22% of test days *[795]*. In areas where HHV-8 infection is endemic, the seroprevalence increases quickly in the first 5 years of life, especially when other family members are HHV-8 positive, then plateaus until adolescence and young adult years. From a study in rural Tanzania, the rate of positivity for HHV-8 was 3.7% among infants, 58% among children aged 4 to 5 years, and 89% in adults aged >45 years *[796]*. The incidence among infants and children increased with the number of HHV-8 positive parents and siblings in the home, indicating nonsexual transmission for prepubertal children, with a limited role for perinatal transmission *[796-802]*.

In the United States, among a cohort of high-risk HIV-infected and HIV-negative adolescents with a median age of 19 years, 11.2% were HHV-8 positive *[803]*. The highest rates were in adolescent HIV-infected males reporting sex with males (23%). Seropositivity was associated with HIV infection, men who have sex with men, a history of syphilis, and injection drug use *[803, 804]*.

HHV-8 may also be transmitted through exposure to infected blood. Adult injection drug users have an increased rate of HHV-8 positivity *[803, 804]*. In addition, recent evidence suggests that HHV-8 may be transmitted through blood product transfusions. In one study from an area of Uganda with a high incidence of HHV-8 seropositivity, the excess risk of acquiring HHV-8 via transfusion was nearly 3%, when comparing recipients of HHV-8 antibody positive blood to those receiving HHV-8 negative blood *[805]*.

A small study suggested that maternal HHV-8 infection might increase the risk for perinatal transmission of HIV, although no evidence of HHV-8 infection was identified among HIV-infected infants *[800]*. Women coinfected with HHV-8 and HIV had increases in both HHV-8 and HIV viral load in serum and/or cervical fluid during pregnancy *[806]*.

In the pre-HAART era, the overall incidence of KS among HIV-infected adults was as high as 20%. The rate among pediatric patients, however, was quite low. In the United States and England, KS represented <1% of pediatric AIDS-defining illnesses.

The incidence of KS appeared to decline even before the widespread use of HAART. The reason for this decline was unclear, but may have been related to the use of other antiviral agents, such as those used to treat CMV (foscarnet, ganciclovir, and cidofovir), which may inhibit HHV-8 *[807-813]*. KS, primary effusion lymphoma, and multicentric Castleman's disease are described most frequently among HIV-infected persons with more advanced immunosuppression (CD4 count of <200 cells/mm^3), although they can occur at any CD4 count. With the advent of earlier and more aggressive HAART, the incidence of KS in adults has continued to decrease *[814]*.

Although KS occurs primarily in adults, the incidence in children has increased substantially as a result of the HIV pandemic, particularly in Africa, and the frequent use of immunosuppressive drugs. One series reported a 40-fold increase in incidence of childhood KS in Uganda in the era of AIDS *[815]*.

Clinical Manifestations

A febrile illness with mild respiratory symptoms and a maculopapular rash has been associated with primary infection in young immunocompetent children *[816]*. A similar self-limited illness has been described in adults with primary infection. There is suggestive evidence of more significant symptomatology among immunodeficient adults with primary infection, including reports of fever, arthralgia, splenomegaly, and bone marrow suppression *[817, 818]*.

KS presentation varies widely, but most persons have nontender, purplish, indurated skin lesions; intraoral lesions can be seen and visceral dissemination can occur, occasionally without the presence of skin lesions. Multicentric Castleman's disease presents with generalized adenopathy and fever and may progress to multiorgan failure.

Diagnosis

The laboratory diagnosis of HHV-8 is most commonly based on serologic assays, such as immunofluorescence, ELISA, and western blot. However, without a standard for diagnosis of HHV-8 infection, these tests range in sensitivity from 80% to ≥90% and demonstrate poor interassay agreement *[819]*. Combination assays containing both lytic and late phase antigens may improve detection rates. Nucleic acid-based tests, such as *in situ* DNA hybridization and PCR, are important for pathologic diagnoses in biologic specimens. Although these tests have high levels of sensitivity, specificity and reproducibility are highly variable. Routine screening for HHV-8 by PCR or serologic testing is not indicated for HIV-infected persons.

Prevention Recommendations

Preventing Exposure

For HIV-infected individuals, coinfection with HHV-8 places them at risk for KS. The risk is highest in adults (compared to children) and for those with severe immunodeficiency. As routine testing of children and adults for HHV-8 is not recommended, the serostatus of newly identified HIV-infected individuals is generally not known. For adolescents diagnosed with KS, counseling should include the possibility of the transmission of HHV-8 to their sexual contacts through intercourse and possibly kissing. Although efficacy of condom use for preventing HHV-8 exposure has not been established, HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce exposure to sexually transmitted pathogens. HIV-infected injection drug users should be counseled not to share drug-injection equipment, even if both users are already HIV-infected, because of the chance of becoming infected with HHV-8 or other bloodborne pathogens.

In the future, HHV-8 testing of donated blood products prior to use for immunodeficient patients might be considered. In addition, the routine use of leukocyte reduction for red cell transfusions may lower the transmission risk.

Infants may acquire HHV-8 perinatally or through contact with infected family members and playmates. There is no effective way known to intervene to prevent childhood acquisition of HHV-8.

Preventing First Episode of Disease

The use of HAART with suppression of HIV replication has led to a marked decrease in the incidence of KS among HIV-infected adults and should be the goal of treatment wherever possible **(BII)**. Routine testing to identify HHV-8-seropositive HIV-infected individuals is not recommended at this time **(DIII)**. Although several antiviral agents inhibit HHV-8 replication *in vitro* (e.g., ganciclovir, foscarnet, cidofovir) there are no data on their use to prevent KS in HIV/HHV-8-coinfected individuals.

Treatment Recommendations

Treatment of Disease

As the HIV-related clinical entities associated with HHV-8, such as KS and Castleman's disease, are oncologic in nature and traditionally have been treated with cytotoxic chemotherapy, specific treatment is not included in this report. However, effective suppression of HIV replication with HAART among HIV-infected patients with KS might prevent progression or occurrence of new lesions and should be considered for all persons with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders **(BII)**.

In HIV-infected adults, HHV-8 cellular viremia and higher viral load have been associated with disease progression *[820]*. The use of specific antiviral agents, such as ganciclovir, foscarnet, and cidofovir, which have *in vitro* activity against the lytic but not latent phase of HHV-8, to treat has not been widely studied. Additionally, the vast majority of infected cells are not undergoing lytic replication and antiherpes medications have had little or no effect on established KS or HHV-8 cellular viremia. Efforts to induce lytic replication or to attack the episomal (latent) HHV-8 genome are in progress *[821, 822]*.

In contrast to KS, many of the cells in Castleman's disease support lytic replication of HHV-8, and treatment of Castleman's disease with antiherpesvirus drugs has led to substantial clinical improvement in some studies *[822]*. The use of intravenous ganciclovir or oral valganciclovir is recommended for the treatment of multicentric Castleman's disease **(BII)** *[823]* and may be a useful adjunctive therapy in the treatment of primary effusion lymphoma **(BII)** *[824, 825]*. Appropriate chemotherapy, in combination with potent antiretroviral therapy, should be considered for patients with visceral KS or primary effusion lymphoma **(BII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

There have been reports of rapid progression of KS following initiation of HAART and following a change from a failing regimen to a more potent one. Progression of KS, representing IRIS, generally appeared within 8 weeks of starting a potent HAART regimen. Most patients experienced a rapid progression of cutaneous lesions, although there are several reports of sudden worsening of pulmonary KS, with resultant deaths in at least four patients. All reported fatalities were linked to pulmonary KS. In most cases, HAART was continued with stabilization and then regression of lesions. In more severe cases, especially those involving visceral lesions, chemotherapy was instituted and, in combination with HAART, led to regression of the KS *[826, 827]*.

Management of Treatment Failure

Prevention of Recurrence

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

Discontinuing Secondary Prophylaxis

Not applicable.

Herpes Simplex Virus

Epidemiology

HSV-1 and -2 affect all populations. HSV-1 is transmitted primarily through contact with infected oral secretions, while HSV-2 is acquired primarily through contact with infected genital secretions. In developed countries, HSV-1 is acquired at a younger age among urban poor populations, with 70% – 80% of individuals seropositive by age 20, compared to only 30% – 40% among the rest of the population. In a large study in the United States, HSV-1 seroprevalence in children aged 6 to 13 years was 31% and increased with age, from 26% in 6- to 7-year-old children to 36% in 12- to 13-year-old children, and varied by race/ethnicity, birthplace, and poverty levels (higher in non-Hispanic blacks, children born in Mexico, and those living below poverty level) *[828]*. The seroprevalence of HSV-1 approaches 60% among the general older adult population *[829]*. HSV-2 seroprevalence in persons aged 14 to 49 years was 17% and increased with age, from 2% in 14- to 19-year olds to 26% in 40- to 49-year olds. HSV-2 seroprevalence was higher in non-Hispanic blacks, those with large numbers of sexual partners, and in females and varied by birthplace and poverty levels *[829, 830]*.

HSV can be transmitted from an HSV-infected mother to her infant resulting in neonatal infection, in addition to the classic person-to-person HSV transmission observed among older children and adults through direct contact with infected oral secretions or lesions. Neonatal HSV infection occurs at a rate of 1 case per 2,000 – 15,000 deliveries *[831]*. Neonatal transmission occurs primarily through exposure of the infant to HSV-infected maternal genital fluids during passage through the birth canal, by ascending infection, or through use of invasive procedures, such as fetal scalp monitoring, that disrupt fetal skin integrity during labor *[832]*. Congenital (*in utero*) HSV acquisition is rare but can result in devastating cutaneous, ocular, and CNS damage.

Maternal HSV antibody status before delivery influences both the severity and the likelihood of transmission to the infant *[832]*. The risk for neonatal HSV infection is greatest when an infant is born to a woman with primary HSV infection (range: 30% – 50%) *[833]*. The risk is much lower (0% – 5%) for infants born to women shedding HSV caused by reactivated infection *[587]*. Genital shedding of HSV at the time of delivery is associated with increased risk for transmission, and prolonged rupture of membranes (>6 hours) also increases the risk for HSV transmission to the infant, probably as a result of ascending HSV infection from the cervix. Cesarean delivery substantially lowers the risk for transmission *[832-834]*. Importantly, many of the mothers of neonates with HSV-related illness will have neither a history of past HSV infection nor of primary lesions during the pregnancy *[832]*. In the United States, 75% of neonatal infections are caused by genital herpes, HSV type 2, and the remainder by HSV type 1.

In a study of seroprevalence among pregnant women in the United States, overall HSV-1 seroprevalence was 63%; HSV-2 seroprevalence was 22%; infection with both HSV-1 and -2 was 13% *[835]*. HSV seroprevalence differed by race/ethnicity and number of lifetime sex partners. HSV-2 infection rates might be higher in HIV-infected than HIV-uninfected women. Women infected with HIV, particularly those with low CD4 count, shed HSV from the vulva and cervix more commonly than women not infected with HIV; the majority of this shedding is asymptomatic *[587, 836]*. Among women who are not infected with HIV, the rate of HSV reactivation is about 25% during the last month of pregnancy, but only about 2% – 3% will be shedding on the day of delivery *[837]*. In comparison, in women who are coinfected with HIV and HSV, an estimated 10% have cervical shedding of HSV on the day of delivery *[838]*. The risk for genital HSV reactivation and shedding increases as HIV-related immunosuppression progresses *[836, 838]*. No evidence exists to indicate that *in utero* HSV infection of the infant occurs more frequently in the HIV-infected pregnant woman or if infants born to women coinfected with HIV/HSV-2 have an increased risk for perinatal (intrapartum) HSV infection. However, HSV infection may increase the risk of mother-to-child HIV transmission. In a study in Kenya, the presence of HSV-2-

related genital ulcers in late pregnancy in women receiving zidovudine prophylaxis was associated with increased plasma HIV RNA levels and an increased risk of intrapartum HIV transmission, even after adjustment for plasma HIV RNA levels *[839]*.

Recurrent or persistent HSV infection is the AIDS-indicator condition in approximately 6% of pediatric AIDS cases. In a study in HIV-infected children in the United States in the HAART era, the incidence of systemic HSV opportunistic infection was 0.9 per 100 child-years and was most common among children with reduced CD4 count (<25%) *[3]*. As in HIV-infected adults, HIV-infected children have more frequent and severe episodes of HSV reactivation. From 5% to 10% of children with AIDS and primary gingivostomatitis develop frequent recurrences, which can be associated with severe ulcerative disease and symptoms similar to primary infection *[840]*. Children with HIV infection also can have more prolonged shedding of virus with both primary and reactivation HSV infection than children without HIV infection.

Clinical Manifestations

Neonatal HSV can appear as disseminated multiorgan disease (occurring in approximately 25% of neonates with HSV infection); localized disease of the CNS (approximately 35% of neonates); or disease localized to the skin, eyes, and mouth (SEM) (approximately 40% of neonates) *[841]*. Infants with disseminated disease usually present at age 9 to 11 days; encephalitis occurs in 60% – 75% of these infants. Vesicular rash is present in approximately 80% of children with localized SEM disease but only in approximately 60% of children with CNS or disseminated disease *[841, 842]*. Localized disease generally presents by the tenth day of life, and even with treatment, neonates with skin lesions commonly have cutaneous recurrences during the first 6 months after treatment *[841]*. Infants with localized CNS disease, or CNS disease with SEM, are generally ill by day 16 to 19 of life *[842]*. 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 have later neurologic sequelae after apparently successful treatment *[843, 844]*.

Outside of the neonatal period, the most common appearance of HSV infection in children is orolabial disease. Fever; irritability; tender submandibular lymphadenopathy; and superficial, painful ulcers in the gingival and oral mucosa and perioral area characterize primary HSV gingivostomatitis. HIV-infected children who experience primary infection when they are immunocompromised can have severe local lesions or, more rarely, disseminated HSV with visceral involvement and generalized skin lesions with primary infection. Other sites of involvement among HIV-infected children with severe immunocompromise include the esophagus, CNS, and genitals and disseminated disease involving the liver, adrenals, lung, kidney, spleen, and brain.

HSV genitalis is the more common manifestation of HSV-2 infection. Painful, ulcerative lesions on the perineum as well as on vaginal and urethral mucosal surfaces are common during primary infection. Local symptoms include a sensory prodrome consisting of pain and pruritis. Mucosal disease is generally accompanied by dysuria, or vaginal or urethral discharge; inguinal lymphadenopathy, particularly in primary infection, is common with perineal disease *[845]*.

HSV keratitis, neonatal HSV, HSV encephalitis, and herpetic whitlow are similar in presentation and treatment to those diseases observed in HIV-seronegative persons but might be more severe. HSV retinitis occurs as acute retinal necrosis, occasionally in the setting of HSV encephalitis. HSV encephalitis occurs among HIV-infected persons, but no evidence indicates that it is more severe or common than among HIV-uninfected persons.

Diagnosis

Clinical diagnosis is based on the typical appearance of vesicles and ulcers. The virus can be isolated in culture and can usually be detected in tissue culture cells within 1 to 3 days. HSV DNA by PCR can also be utilized to establish the presence of HSV infection in skin lesions or infected mucosal sites of perinatally exposed newborns. For the diagnosis of neonatal HSV infection, specimens for HSV culture or HSV DNA PCR should be obtained from blood and skin vesicles, mouth or nasopharynx, eyes, urine, and stool or rectum; positive cultures from any of the latter sites >48 hours after birth indicate viral replication rather than contamination after intrapartum exposure. CSF should be tested for HSV DNA by PCR amplification of an HSV DNA sequence common to both HSV-1 and HSV-2.

Direct immunofluorescence for HSV antigen can be conducted on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Giemsa staining (Tzanck preparation) of lesion cell scrapings might show multinucleated giant cells and eosinophilic intranuclear inclusions, but this test is insensitive and nonspecific and is not routinely recommended.

Among children with suspected HSV encephalitis, cultures of the CSF for HSV are usually negative. Detection of HSV DNA by PCR in the CSF has replaced brain biopsy as the diagnostic test of choice in such patients. The sensitivity of the CSF PCR in neonatal CNS HSV disease has been reported to be between 75% and 100%, with the specificity ranging from 70% to 100% *[846]*. During therapy for HSV-proven encephalitis, the CSF HSV PCR remains positive for a mean of 10 days *[847]*.

Definitive diagnosis of HSV esophagitis requires endoscopy with biopsy (histologic evidence of multinucleated giant cells with intranuclear viral inclusion) and culture.

Prevention Recommendations

Preventing Exposure

The rate of HSV transmission to the fetus and neonate among HIV-infected pregnant women coinfected with HSV is not known. Although isolated cases of *in utero* HSV transmission with primary infection during pregnancy among HIV-uninfected women have been reported, the predominant risk, regardless of HIV coinfection, is from maternal genital shedding at delivery. Effective HAART regimens may decrease, but not prevent, the frequency of maternal genital HSV shedding and recurrence of genital lesions *[848]*.

Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and shedding in late pregnancy among HIV-uninfected women with HSV infection and appears to reduce the need for cesarean delivery for recurrent HSV *[849-851]*. However, the safety and efficacy of this strategy have not been evaluated among HIV-infected women who are more likely to have antibody to HSV-2 and to have both symptomatic and asymptomatic reactivation of genital HSV. Therefore, the use of acyclovir or valacyclovir specifically to reduce the need for cesarean delivery among HIV/HSV-coinfected women is not recommended **(DIII)** *[852]*. In addition, there are case reports of HSV-infected neonates born to women who received suppressive antiviral therapy near term *[853]*.

For pregnant women with active genital HSV at the onset of labor, delivery by elective cesarean section, preferably prior to rupture of membranes, is recommended *[854]* **(AI)**.

For the HIV-infected child, exposure to HSV-1 is an inevitable part of childhood, and there are no proven ways of preventing exposure. Direct contact of children with secretions from active HSV lesions (such as herpes labialis) on the mother, household, or other individuals should be avoided.

Among sexually active, HIV-infected adults, latex condoms should be used during every act of sexual intercourse to reduce the risk for exposure to HSV and to other sexually transmitted pathogens **(AII)**. They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident **(AII)**. There are data to suggest that chronic suppressive therapy with valacyclovir in persons with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50%. In HIV-infected adults, HAART was found to reduce the frequency of symptomatic herpetic lesions compared to adults not on HAART, but mucosal HSV-2 shedding was similar *[855]*.

Preventing First Episode of Disease

Antiviral prophylaxis after exposure to HSV or to prevent initial episodes of HSV disease among persons with latent infection is not recommended **(DIII)**.

Treatment Recommendations

Treatment of Disease

Acyclovir is the drug of choice for treatment of local and disseminated HSV among infants and children, regardless of HIV-infection status **(AI)**. Both oral and intravenous preparations are available. Neonatal HSV disease should be treated with high-dose intravenous acyclovir (20 mg/kg/dose three times daily) administered for 21 days for CNS and disseminated disease and for 14 days for SEM disease *[856]* **(AI)**. Acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay is negative near the end of treatment **(BIII)**. Orolabial lesions in HIV-infected children can be treated with oral acyclovir for 5 to 10 days **(AI)**. Moderate-to-severe mucocutaneous HSV lesions are best treated initially with intravenous acyclovir **(AI)**. Patients may be switched to oral therapy after the lesions have begun to regress, and therapy continued until lesions have completely healed. Acyclovir is the drug of choice for disseminated HSV and HSV encephalitis in children. Regardless of age, HSV encephalitis should be treated for 21 days **(AII)**. Genital HSV should be treated with oral acyclovir for 5 to 14 days **(AI)**. Trifluridine, a fluorinated pyrimidine nucleoside, is the treatment of choice for herpes keratoconjunctivitis, one drop onto the cornea *[857]* every 2 hours, not to exceed nine drops/day; it is not recommended for longer than 21 days **(AII)**.

Alternatives to acyclovir in older adolescents and adults include valacyclovir and famciclovir **(AI)** *[858-861]*. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption. Data are limited on valacyclovir in children *[862]*; bioavailability is about 45% and independent of age in children. Based on limited available data, pediatric blood levels of acyclovir (from the prodrug valacyclovir) similar to levels achieved with valacyclovir tablets in adults can be achieved by administering an oral dose of valacyclovir of 20 − 25 mg/kg/dose given two to three times a day *[863]*. However, no pediatric formulation is available, and hence this drug is an alternative only for children old enough to swallow the large valacyclovir tablets. Although tablets can be crushed, they have a very unpleasant taste. There are no specific data on the pharmacokinetics and dosing of famciclovir in children and no pediatric preparation is available *[863]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

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. Toxicities are similar for valacyclovir. In infants receiving high-dose acyclovir for neonatal disease, the major toxicity was neutropenia (e.g., absolute neutrophil count <1,000/mm^3) *[856]*. Grade 3 or higher nephrotoxicity was observed in 6%. For children receiving high-dose IV acyclovir, monitoring of complete blood counts and renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction or those receiving prolonged therapy.

Management of acyclovir-resistant herpes with foscarnet is associated with decreased renal function; ≤30% of patients experience increases in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions such as calcium lead 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. For patients receiving foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter **(AIII)**.

Atypical lesions that may have a delayed response to therapy have been reported in adults initiating HAART and attributed to IRIS *[855]*.

Management of Treatment Failure

Treatment failure related to resistance to antiviral drugs should be suspected if lesions do not indicate signs of resolution within 7 to 10 days after initiation of therapy. Among immunocompromised patients with suspected acyclovir-resistant HSV, a lesion culture should be obtained and, if virus is isolated, susceptibility testing performed to confirm drug resistance *[857]*.

The treatment of choice for acyclovir-resistant HSV is intravenous foscarnet *[857, 864]* **(AI)**. All acyclovir-resistant HSV strains are resistant to valacyclovir and most are resistant to famciclovir. Topical trifluridine or cidofovir also have been used successfully for lesions on cutaneous surfaces, although prolonged application for 21 to 28 days or longer might be required *[865]*. Intravenous cidofovir has been used to treat a child with acyclovir- and foscarnet-resistant HSV *[866]*.

Prevention of Recurrence

Following neonatal HSV infection, administration of oral acyclovir prevented cutaneous recurrences of HSV after neonatal SEM disease, but the effect of such therapy on neurologic outcome needs assessment, and additional investigation is necessary before routine use of suppressive therapy in this population can be recommended *[844]*.

Because episodes of HSV disease can be treated successfully, chronic therapy with acyclovir is not required after lesions resolve. However, children who have frequent or severe recurrences (e.g., >3 to 6 severe episodes a year) can be administered daily suppressive therapy with oral acyclovir **(AI)** *[863]*. Valacyclovir or famciclovir also are options for older children **(AI)**. Effective HAART therapy may also lessen the frequency of recurrences.

Discontinuing Secondary Prophylaxis

Not applicable, secondary prophylaxis not generally recommended in children.

Human Papillomavirus (HPV)

Epidemiology

Human papillomavirus (HPV) infects cutaneous and mucosal squamous epithelium. More than 100 distinct types of HPV exist *[867]*. They can be categorized on the basis of the site at which they occur (genital vs cutaneous) and as high or low risk on the basis of their potential to induce malignant proliferation. There are approximately 40 genital (i.e., muscosal) HPV types of which 12 types are identified as established high risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and 6 probable high risk (HPV 26, 53, 66, 68, 73, 82) *[867]*. Genital HPV types can infect the genitals, conjunctiva, mouth, throat, and respiratory tract. Nongenital (i.e., cutaneous) HPV types that cause skin warts (such as HPV 2) are distinct from those causing genital infections. Children with compromised cellular immunity might have intense and widespread appearance of both cutaneous and mucosal warts.

Transmission of HPV-associated cutaneous warts occurs by close person-to-person contact and might be facilitated by minor trauma to the skin. HPV-associated anogenital warts are transmitted by sexual contact but also might be acquired at the time of delivery or transmission from nongenital sites. Genital warts (condyloma accuminatum) in young children might be a sign of sexual abuse *[868, 869]*.

Mother-to-child transmission of HPV is not surprising since high rates of HPV are found in pregnant women *[870, 871]*. HPV DNA has been identified in 5% – 42% of pregnant women without HIV infection *[872-874]*. Although a few studies have demonstrated an increased prevalence of detectable HPV DNA during pregnancy, this finding has not been consistent across all studies *[873, 874]*. Among nonpregnant women, HPV DNA is detected more frequently among HIV-infected than uninfected women, with reported prevalence rates ranging from 12% to 77% *[875, 876]*. Few data have been reported related to HPV prevalence in HIV-infected pregnant women, with one study reporting a prevalence of 35% *[877]*.

HPV DNA has been detected in cord blood and amniotic fluid, indicating the potential for *in utero* infection *[878, 879]*. Duration of membrane rupture has been associated with mother-to-child HPV transmission, and reports of HPV transmission to infants born by cesarean section suggest that HPV can cross the placental barrier *[880, 881]*. Most transmission studies report on the detection of HPV DNA since clinical disease (i.e., warts) is rare in infants. Reported rates of HPV DNA detection in nasopharyngeal aspirates, buccal brush swabs, or genital swabs from infants born to HPV-infected mothers have varied, ranging from 2% to 80% *[870, 871, 880]*. In general, neonatal clinical abnormalities at birth are extremely uncommon. Genital condyloma can occur within weeks to months after birth but are rare. Respiratory papillomatosis, a rare condition in which respiratory papillomas develop and typically recur (i.e., juvenile onset recurrent respiratory papillomatosis), usually manifests within 2 to 5 years after birth. Respiratory papillomatosis in children is thought to be secondary to HPV transmitted from mother to child through aspiration of infectious maternal genital secretions during delivery, although other methods of transmission are possible *[870]*. A recent parent-child study found that the cumulative detection rate for high-risk HPV from the child's genital samples was 53% over 3 years but only 1.5% showed persistence. HPV was detected more commonly from oral samples with a cumulative rate of 63% with 10% persistence *[870]*. Persistence in infant oral samples was associated with persistent oral HPV detection in the mothers. Persistent genital infections were associated with the mother's history of having genital warts. The prevalence of HPV DNA in the oropharynx in >1,000 children in Iowa was assessed in one study; a bimodal age distribution was found with highest HPV prevalence in the youngest and oldest groups: 2.5% at age <1 year, 0.8% at age 1 to 4 years, 1.2% at age 5 to 11 years, 1.5% at age 12 to 15 years, and 3.3% at age 16 to 20 years *[882]*. These data support the high rate of HPV clearance in children even if the infant is exposed to HPV during infancy.

Although perinatal transmission is possible, genital HPV is most commonly sexually transmitted. Young age and number of recent sexual partners are strong risk factors for the acquisition of HPV *[883-887]*. Prevalence of HPV is very common in sexually active adolescent girls, with prevalences ranging from 12% to 64% compared to 2% – 7% in women >35 years of age *[884, 888-890]*. Acquisition of cervical HPV occurs shortly after the onset of sexual activity with 50% cumulative exposure within 3 years *[883, 885]*, even among young women with one sexual partner *[891]*.

Although the incidence of anogenital HPV infection in sexually active youth is high, longitudinal studies have demonstrated that 80% – 90% of infections among youth without HIV infection might be transient and spontaneously regress *[889, 892]*. Although repeated infections with new types are common *[888]*, it is not known whether repeat detection of same HPV-type infections are due to new exposures or due to reactivation of latent infection *[893]*. Although the prevalence of HPV has consistently been higher among HIV-infected men and women, acquisition rates of HPV seem to be similar among the HIV infected and uninfected *[894]*. The higher prevalence is due to the increased rate of HPV persistence observed in HIV-infected persons. In one study of adolescents with HIV, only 50% cleared their HPV infections *[894]*. Other possible risk factors for persistence have included multiple types or high-risk types of HPV (e.g., 16 and 18), older age, smoking cigarettes, and duration of HPV detection for >12 months *[895]*. Detection of anal HPV is also higher among HIV-infected youth *[896]*. Receptive anal sex is a risk for anal HPV among HIV-infected and -uninfected men; the association between anal HPV infection and anal sex is not as clear for women *[896, 897]*. In one study of HIV-infected women, anal HPV infection was found more prevalent than cervical infection *[898]*.

Persistent infection with high-risk HPV is associated with an increased risk for developing cervical and anal intraepithelial neoplasia and risk for cervical, vulvovaginal, and anal carcinoma in both women and men. All these HPV-associated cancers are found at higher rates among HIV-infected persons *[899]* and are thought to be predominantly due to the increased risk of persistence in this group. Interestingly, the risk for these HPV-associated cancers is highest among young persons with HIV *[899]*. Adolescent girls have biologic differences from adult women (e.g., cervical squamous metaplasia) that might increase their susceptibility to either development of persistent infection or disease *[876, 900]*. The risk for HPV-associated cervical abnormalities is increased among HIV-infected youth. In one study, 33% of HPV-infected youth with HIV progressed to high-grade squamous intraepithelial lesions (HSIL) within 3 years of observation *[901]*. CD4 immunosuppression was correlated with HPV persistence but not the development of HSIL. While HAART has dramatically altered HIV natural history, its impact on HPV and HPV-associated neoplasia is less clear. Other risks associated with the development of cervical cancers include lack of cervical cancer screening, prolonged hormonal contraceptive use, parity, use of tobacco products, and immunocompromising conditions (besides HIV) *[887]*.

Clinical Manifestations

Genital HPV types cause hyperplastic, papillomatous, and verrucous squamous epithelial lesions on skin and mucus membranes, including anal, genital, oral, nasal, conjunctiva, GI, bladder, and respiratory tract mucosa. Wart lesions can appear as papules or flat, smooth, or pedunculated lesions. Sometimes they can be soft, pink, or white "cauliflower-like" sessile growths on moist mucosal surfaces (condyloma accuminatum) or keratotic lesions on squamous epithelium of the skin with a thick, horny layer. Since HPV requires access to basal epithelial cells through disruption of the squamous epithelium, common sites for skin warts are the hand, elbows, knees, and feet.

Diagnosis

Most cutaneous and anogenital warts can be diagnosed by physical examination. Diagnosis of laryngeal papillomas requires laryngoscopy, and children with suspected respiratory tract papillomas need to be evaluated by a pediatric otolaryngologist.

It remains debatable whether all cervical HPV infections result in microscopic abnormalities described as squamous intra-epithelial lesions (SIL). The majority of HPV DNA detected from cervical samples is associated with normal cervical cytology. These infections either have microscopic lesions not detected by the insensitive cytologic test or are truly latent. The Pap test (conventional or liquid based) is a screening test for HPV-associated disease, including cervical cancer. However, histology remains the current gold standard for the detection of HPV-associated cervical and anal precancerous lesions and invasive cancers.

Biopsies for histologic diagnosis are usually directed by colposcopy or high-resolution anoscopy. There are no screening tests for vaginal and vulvar disease; however, these lesions are often diagnosed in those referred to colposcopy for abnormal cytology or because of abnormalities noted on macroscopic examination. Histologic confirmation should also be made for vulvar and vaginal SIL and cancer.

HPV DNA can be detected using several platforms *[902, 903]*. The only FDA-approved test is HybridCapture™, which detects any of 13 high-risk HPV types and is not type specific. Detection and typing of HPV is not recommended for diagnosis or management of anogenital or cutaneous warts or papillomas *[869]*. HPV testing is not recommended in any circumstance for adolescent girls, 20 years and younger *[904]*. This is true for both HIV-infected and -uninfected adolescents due to the high rates of HPV infection. These recommendations may change once specific HPV testing has been studied in clinical trials.

Prevention Recommendations

Preventing Exposure

HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce the risk for exposure to sexually transmitted pathogens **(AII)**, including HPV *[886]*.

HPV Vaccine

In June 2006, the FDA approved the first preventive vaccine for HPV types 16, 18, 6, and 11. HPV 16 and 18 cause almost 70% of invasive cervical cancers and HPV 6 and 11 cause 90% of external genital warts. HPV exposure is extremely common after sexual contact, not just sexual intercourse, is initiated. Administration of the vaccine is critical before the onset of sexual activity for it to be fully effective. Data for women without HIV infection showed efficacy rates of 95% for preventing HPV infection and high-grade CIN related to vaccine-related HPV strains and 99% efficacy for genital warts *[905, 906]*. However, if there was documented previous exposure to the vaccine HPV types, no efficacy was noted for that type, underscoring the fact that the vaccine is not therapeutic. A second vaccine targeting HPV 16 and 18 has had similar efficacy (Cervarix, GSK) *[907]* and is expected to receive FDA approval in 2008.

Although considered safe, studies in HIV-infected persons are not yet available, so immunogenicity and efficacy in this population have not yet been established. However, because quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications, including HIV-infected females. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent *[30, 908]* (Figure 2). Studies of the immunogenicity of HPV vaccine are ongoing in HIV-infected females. Current CDC recommendations for HPV immunization for all children and adolescents should be followed for HIV-infected as well as uninfected individuals *[908]*. The first dose of the HPV vaccine series should be administered to females aged 11 to 12 years but can be administered as early as 9 years. The second dose should be administered 2 months after the first dose and the third dose should be administered 6 months after the first dose. HIV-infected females aged 13 to 18 years who have not been previously vaccinated

should also be vaccinated with the three-dose HPV vaccine series.

The HPV vaccine has not been shown to have any therapeutic benefit to treat existing HPV-related lesions in either HIV-infected or -uninfected women. There are no published studies using the HPV vaccine to prevent HPV infection and associated lesions of the anus, penis, or oral cavity in men and the vaccine is not currently approved for use in men in the United States. As in HIV-infected women there are no data on the safety or efficacy of the HPV vaccine in HIV-infected men.

Preventing First Episode of Disease

HPV-Associated Genital Epithelial Cancers among HIV-Infected Women

After a complete history of previous cervical disease has been obtained, HIV-infected sexually active women should have a pelvic examination and a cervical cancer screening test (Pap test, either conventional or liquid based). In accordance with the recommendation of the Agency for Health Care Policy and Research, the Pap smear should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter **(AII)**. If the results of the Pap smear are abnormal, care should be provided according to treatment guidelines described for adolescents below. Adult women (e.g., aged >20 years) should be managed according to adult guidelines. No data are available to demonstrate that these guidelines to prevent cervical disease should be modified for women on HAART.

HPV-Associated Anal Intraepithelial Neoplasia and Anal Cancer among HIV-Infected Men Who Have Sex with Men and among Women

Evidence from multiple studies demonstrates that HIV-infected men who have sex with men, and HIV-infected women are at increased risk for anal HSIL and might be at increased risk for anal cancer. In view of this evidence, and given a cost-effectiveness analysis projecting that screening and treatment for anal HSILs provide clinical benefits comparable to other measures to prevent OIs among HIV-infected persons *[909]*, anal cytology screening of HIV-infected men who have sex with men and of women might become a useful preventive measure *[910]*. However, studies of screening and treatment programs for anal HSILs need to be implemented before recommendations for anal cytology screening can be made.

Treatment Recommendations

Treatment of Disease

Genital Warts

Multiple treatments for HPV-associated skin and external genital lesions exist; however, no single treatment is ideal for all patients or all lesions **(CIII)** *[869]*. 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. No data suggest that treatment modalities for external genital warts should be different in the setting of HIV infection. However, persons who are immunosuppressed because of HIV might have larger or more numerous warts, might not respond as well as immunocompetent persons to therapy for genital warts, and might have more frequent recurrences after treatment *[153, 911, 912]*. In addition, topical treatments are seldom effective in patients with large or extensive lesions. Topical treatments include podofilox (0.5 %) solution or gel (antimitotic agent), imiquimod (5%) cream (topical immune enhancer that stimulates production of interferon and other cytokines), trichloroacetic or bichloroacetic acid (80% – 90% aqueous solution) (caustic agents that destroy warts by chemical coagulation of proteins), and podophyllin resin (10% – 25%) in a compound tincture of benzoin (contains antimitotic compounds and mutagens). Podofilox and imiquimod are patient applied. Podofilox is applied to all lesions twice a day for 3 consecutive days, followed by 4 days of no therapy. This cycle can be repeated weekly up to 4 weeks **(BIII)**. Imiquimod is applied once daily at bedtime three times a week for up to 16 weeks. The treatment area should be washed with soap and water

the following morning **(BII)**. Acid cauterization (i.e., tricholoracetic or bichloroacetic acid) 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 consecutive 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)**. Podophyllin resin has lost favor since the production of the resin can vary in potency and is not reliable.

Other treatments include Veregen (based on the antioxidative effect of green tea extract), intralesion interferon or 5-fluorouracil/epinephrine gel implant, and cidofovir topical gel (1%). Veregen (sinecatechins) is a new FDA-approved topical product for external genital wart treatment that can be used three times daily for up to 16 weeks. No data are available on this treatment for HIV-infected persons **(CIII)**. Cidofovir topical gel (1%) is a topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection **(CIII).** Topical cidofovir may result in systemic absorption and be associated with renal toxicity *[913]*. Injectable therapy (e.g., interferon or 5-fluorouracil/epinephrine gel implant) should be offered in only severely recalcitrant cases due to inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects.

Lesions can be removed by cryotherapy or surgery **(BIII)**. Cryotherapy (i.e., application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1 to 2 weeks up to four times. The major toxicity is local pain. Adequate local pain management for all caustic treatments in children is essential. Topical anesthetics such as EMLA are favored. Surgical removal either by tangential scissor, tangential shave excision, curettage, or electrosurgery can be performed.

Oral Warts

Oral warts may be located on a variety of surfaces in the mouth. In contrast to other oral manifestations of HIV, an increased prevalence of oral warts in patients on HAART has been reported from the United States and the United Kingdom *[914-916]*. There are no randomized trials of treatment of oral warts. Treatments include surgical excision and cryotherapy; some topical modalities have had success *[916]*.

Respiratory Papillomatosis

Respiratory papillomatosis should be managed by a specialist *[917]*. 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 with limited success in children with frequent recurrences or extension into the trachea, bronchi, or lung parenchyma **(CIII)**.

Management of Abnormal Cytology

Management of anogenital HPV infection accompanied by cytologic changes indicating dysplasia/carcinoma among adolescents is slightly altered from that for the adult population. Adolescents aged 13 to 20 years and young women are considered a special population. There is a very low risk for invasive cervical cancer in this group, but CIN lesions are common. As noted earlier, CIN in HIV-uninfected adolescents also has a very high rate of spontaneous regression of CIN lesions *[918]*. HPV testing for follow-up is not recommended for adolescent populations whether HIV infected or uninfected *[904]*.

Because of the high rate of progression to HSIL, it is currently recommended to refer all HIV-infected adolescents with any SIL (LSIL or HSIL) and ASCUS suggestive of HSIL to colposcopy **(BIII)**. In

patients with ASCUS alone, Pap smear for cytology can be repeated in 6 to 12 months. If ASCUS or greater is found on repeat cytology, referral to colposcopy is warranted.

Treatment of Histologic CIN

Follow-up with annual cytological assessment is recommended for adolescents with CIN 1 **(AII)** *[904]*. At the 12-month follow-up, only adolescents with HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24-month follow-up, those with an ASCUS or greater result should be referred to colposcopy **(AII)**.

For adolescents and young women with a histological diagnosis of CIN 2 or 3 not otherwise specified, either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable, provided colposcopy is satisfactory **(BIII)** *[904]*. When a histological diagnosis of CIN 2 is specified, observation is preferred but treatment is acceptable. When a histological diagnosis of CIN 3 is specified or when colposcopy is unsatisfactory, treatment is recommended **(BIII)**.

If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended **(BIII)**. After two consecutive "negative for intraepithelial lesion or malignancy" results, adolescents and young women with normal colposcopy can return to routine cytological screening **(BII)**. Treatment is recommended if CIN 3 is subsequently identified or if CIN 2 or 3 persists for 24 months **(BII)**.

Persistent CIN 1, 2, and 3 lesions in HIV-infected women should be treated as in HIV-uninfected women *[904]*. Conventional therapies used for treatment of CIN 2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). LEEP is generally the preferred mode of treatment **(BIII)**. Recurrence rates of 40% – 60% after treatment have been reported among HIV-infected women undergoing these procedures. Pregnant HIV-infected adolescents should be treated similarly to pregnant HIV-infected adults.

Role of ART

HAART has not been consistently associated with a reduced risk for HPV-related cervical abnormalities in HIV-infected women. However, severe immunosuppression is associated with greater frequency of morbidity and mortality.

Monitoring of Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Monitoring is required during and after treatment of genital warts since each of the treatments has associated toxicity and recurrences are common after treatment. Patients can be monitored by physical examination for evidence of recurrence. The major toxicity of podophyllotoxin and topical podophyllin resin is local skin irritation. Also, if podophyllin is applied to a large treatment area, systemic absorption can cause nausea, vomiting, and CNS effects. The major toxicity of imiquimod is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major side effects of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major adverse events associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional interferon can be associated with systemic toxicities of interferon, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation may lead to bleeding and abscess formation. Scarring may occur with any of the above treatment modalities. Topical cidofovir may result in systemic absorption and be associated with renal toxicity *[913]*. Secondary infections are not uncommon if ulcerations occur. Patients should be monitored regularly after each treatment.

Because risk of recurrence of CIN and cervical cancer after conventional therapy is increased among HIV-seropositive persons, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)** *[919, 920]*. Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis.

The major toxicity of topical agents for treatment of external genital warts is local pain or irritation of adjacent normal skin. HIV-infected patients with immunosuppression might have a lower response rate to all of these modalities. Secondary infections are not uncommon if ulcerations occur. Patients should be monitored regularly after each treatment.

Because of the frequent recurrence of SIL after treatment, close surveillance with colposcopy and cytology is recommended.

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 RNA levels with HAART *[914]*. Immune reconstitution in response to viral load reduction might result in a return of marked inflammatory responses against latent oral HPV infection.

Management of Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed **(AIII)**. Genital warts often require more than one course of treatment. Recalcitrant warts should be managed by experienced clinicians and referred for excisional therapy. Recurrence of CIN may require additional treatments (i.e., LEEP, laser).

Prevention of Recurrence

There are no recommendations for prevention of recurrence of external genital warts. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions **(AI)** *[909, 921]*. Use of low-dose intravaginal fluorouracil (Efudex) was shown in one study to reduce recurrence of CIN after LEEP but lack of additional studies do not warrant routine use *[922]*. Efudex should not be used in pregnant women.

Discontinuing Secondary Prophylaxis

Not applicable.

Progressive Multifocal Leukoencephalopathy (PML)

Epidemiology

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the CNS seen in immunocompromised patients, first described in association with chronic lymphocytic leukemia and Hodgkin's disease *[923]*. It is caused by primary infection or reactivation of the Jamestown Canyon virus (JCV), a ubiquitous polyoma virus. The majority of humans are infected with JCV early in life; 50% of children are seropositive by 9 to 11 years of age, and seropositivity among adult women aged >25 years is 72% *[924]*. Infection results in chronic asymptomatic carriage in the kidneys, lymphoid tissue, bone marrow, and lymphocytes *[925, 926]*; in a patient with a weakened immune system, the virus may reactivate and spread to the brain by lymphocytes, causing neurologic dysfunction and serious and life-threatening disease.

PML is an AIDS-defining illness in HIV-infected individuals. PML has been rare in reports from large series of HIV-infected children *[1, 4, 927]*, although there have been case reports in children *[928-933]*.

Clinical Manifestations

No known symptoms associated with acute JCV infection exist. PML is the only disease caused by JCV. Cases that have occurred in children are similar to those in adults.

Demyelination is at first patchy, involving subcortical regions, and then spreads to deep white matter in confluent pattern; thus, PML may initially present with focal neurological deficits that can involve different brain regions. The established criteria for clinical diagnosis are focal signs and symptoms on neurological examination, focal white matter lesions on MRI or CT without mass effect, and exclusion of other causes of the clinical and neuroradiological findings *[934]*. The disease has an insidious onset and produces a neurologic syndrome that steadily progresses over weeks or months, characterized by confusion, disorientation, lack of energy, loss of balance, cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, visual abnormalities (e.g., blurred or double vision or loss of vision), hemiparesis or quadraparesis, and eventually coma. In the pre-HAART era, adults and children with PML had extremely poor survival *[927]*. Survival among adults has improved in the HAART era *[935-937]*. There are no comparable data for children.

Diagnosis

A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings coupled with brain biopsy demonstrating a characteristic triad of pathologic foci of demyelination, enlarged hyperchromatic oligodendrocytes with enlarged nuclei and basophilic-staining intranuclear material, and enlarged astrocytes with bizarre hyperchromatic nuclei. When only two of these features are present, JCV may be demonstrated by *in situ* hybridization or by electron microscopy for definitive diagnosis.

Although brain biopsy remains the confirmative test for diagnosis of PML, brain scans such as MRI or CT scans can reveal the presence of lesions in the brain. The radiological features of PML are typically noninflammatory (unless associated with IRIS associated with HAART). Typical CT abnormalities include single or multiple hypodense, nonenhancing cerebral white matter lesions, although cerebellum and brain stem are occasionally involved. An MRI scan depicts white matter lesions of low T1 signal intensity and high proton density on T2 weighted images with absence of edema or mass effects, as might be seen with cerebral toxoplasmosis or lymphoma. Post-contrast enhancement is unusual, and when present, is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions.

PML diagnosis is now facilitated by use of PCR to detect JCV DNA in CSF, which may obviate the need for brain biopsy in patients with a compatible clinical syndrome and radiographic findings. Nested JCV PCR on CSF is highly sensitive (90% – 100%) and specific (92% – 100%) for PML *[938]*. Measurement of JCV DNA levels in CSF samples may be a useful virological marker for management of PML in patients receiving HAART *[939]*.

Prevention Recommendations

Preventing Exposure

There is no known means of preventing exposure to JCV.

Preventing First Episode of Disease

There is no means of preventing the occurrence of PML in severely immune-suppressed persons. The use of HAART can prevent or reverse the development of severe immunosuppression.

Discontinuing Primary Prophylaxis

There is no demonstrated means of primary prophylaxis of JCV infection or the development of PML.

Treatment Recommendations

Treatment of Disease

No established effective therapy of JCV or PML exists. Survival in HIV-infected adults with PML has substantially improved in the post-HAART era, with a median survival increase from 14 to 64 weeks *[940]*. A CD4 count of >100 cells/mm^3 at the time of diagnosis of PML was associated with an improved survival, and the use of HAART post-diagnosis of PML was also strongly associated with an improved survival *[940]*. Thus, the main approach to treatment involves maximally optimizing antiretroviral therapy to reverse the immunosuppression that interferes with the normal host response to this virus **(AII)**.

A number of agents have been proposed or reported anecdotally as more specific treatments for PML, but none of these has been proven effective after greater scrutiny or more extensive study. For PML, there has been a randomized open-label trial of intravenous and intrathecal cytosine arabinoside *[941]* and a nonrandomized, open-label trial of cidofovir *[942]*; neither drug was effective in producing clinical improvement and neither is routinely recommended **(DII)**. Immunomodulatory approaches, such as interferon-alfa, have also been described in case reports in HIV-infected adults, but none have yet been studied in a prospective, controlled clinical trial and in one analysis did not provide any benefit beyond that observed with HAART *[943]*; thus they are also not currently routinely recommended **(DIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Neurologic stability or improvement and prolonged survival are associated with a reduction in JCV DNA and appearance of JCV-specific antibody in CSF of HAART-treated PML patients *[944]*.

When antiretroviral therapy is initiated and CD4 counts rise, certain patients will experience neurologic improvement and others might become neurologically stable; however, reports have documented patients experiencing worsening neurologic manifestations after initiation of HAART *[937]*. In certain instances, this worsening is caused by an IRIS *[937, 945-947]*, examples of which have occurred in children *[21]*. Other cases may represent the natural history of PML. The underlying etiology and trigger of HAART-associated PML is controversial. One hypothesis postulates a reduction in inhibitory cytokines (e.g., interferon-alfa and interleukin-12) after HAART, thus promoting JCV reactivation within the brain or by increasing trafficking of JCV-infected peripheral lymphocytes into the brain *[948]*. JCV infection

occurring coincidental to the time of HAART onset resulting in a beneficial inflammatory response with lack of disease progression is another hypothesis *[948]*, particularly given that JCV in children with perinatal HIV infection would most often be acquired during childhood. The overall prevalence of IRIS in children is not known. Inflammatory PML should be suspected in HAART-treated children with advanced HIV disease who show acute neurologic deterioration and contrast-enhancing demyelinating lesions on MRI.

Management of Treatment Failure

PML remission with HAART may take several weeks and there are no defined criteria to define progression of disease. A working definition used for HIV-infected adults is continued clinical worsening and continued detection of CSF JCV at 3 months (see ***Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults***) *[16]*. As noted, some patients' PML worsens despite the use of HAART, either as a result of IRIS or the natural history of PML. In both cases, HAART should be continued. If there is failure to suppress HIV RNA or to boost the CD4 count with the HAART regimen, then attention should be focused on modifying and optimizing the antiretroviral treatment **(AII)**. However, in HIV-infected children responding well to HAART but with continued worsening PML, consultation with an expert in pediatric HIV infection should be obtained.

Prevention of Recurrence

The main preventive measure, based on its role in reversing the disease, is an effective antiretroviral regimen that suppresses HIV viremia and maintains CD4 count **(AII)**.

Discontinuing Secondary Prophylaxis

There is no demonstrated means of secondary prophylaxis of JCV infection or the development of PML.

Varicella-Zoster Virus (VZV)

Epidemiology

Varicella-zoster virus (VZV) infections occur worldwide. In the prevaccine era, approximately 4 million cases of varicella occurred annually in the United States. Since the institution of universal varicella vaccination for healthy children, the incidence of varicella and its associated morbidity and mortality have decreased by approximately 74% – 90% *[949]*. Varicella has the potential to cause greater morbidity and mortality in HIV-infected individuals than among the general population *[950, 951]*.

VZV causes both varicella (a primary infection) and zoster (a secondary infection), which is due to reactivation of latent VZV acquired during varicella *[952]*. The incubation period of varicella ranges from 10 to 21 days (average of 14 days). Before the widespread use of varicella vaccine in the United States, the annual rate of acquiring varicella in children aged <10 years was 9%; by adulthood >95% of persons had antibodies to VZV, indicating a past history of primary infection *[953]*.

Once established, latency of VZV persists for life. Reactivation, causing clinical zoster, occurs in roughly 25% of people. A decline in specific cellular immunity to VZV contributes significantly to development of zoster *[952]*. HIV-infected persons are at higher risk to develop zoster, by a factor of 15 – 25 times, compared to the general population *[954]*. The incidence of zoster also increases with age, particularly in persons aged >50 years.

VZV is mainly transmitted from skin lesions during illness *[955]*. Varicella is highly contagious; clinical infection develops in about 80% of susceptible individuals exposed in a household *[956]*. Second attacks of varicella are uncommon but can occur *[952]*. Zoster is less contagious than varicella.

Mother-to-child transmission of VZV can occur; however, because most adults are immune, varicella complicating pregnancy is unusual. In one study, 13% of HIV-infected pregnant women lacked immunity to VZV *[957]*. It is unknown whether mother-to-child VZV transmission is increased among HIV-infected pregnant women with varicella. The congenital varicella syndrome occurs in approximately 0.4% (95% CI 0.05% – 1.5%) of infants born to women who have varicella during pregnancy before 13 weeks gestation and in approximately 2% (95% CI 0% – 5%) of infants born to women who have varicella between 13 to 20 weeks gestation *[958]*. This syndrome is not seen among women who develop herpes zoster during pregnancy. Fewer than 100 cases of congenital VZV have been reported, none so far in HIV-infected mothers. However, cases of congenital varicella syndrome may not be recognized. Before availability of varicella vaccine in the United States, 44 cases were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring; limb hypoplasia; and neurologic (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal (e.g., hydroureter, and hydronephrosis), and autonomic nervous system abnormalities (e.g., neurogenic bladder, swallowing dysfunction, and aspiration pneumonia) *[959-961]*.

VZV can be transmitted to the fetus in later gestation, resulting in acute neonatal varicella. When the mother develops varicella from 4 days before to 2 days after delivery without passive antibody prophylaxis, the attack rate for infants is approximately 20% and mortality, before availability of antiviral therapy, was approximately 30% *[959]*. In comparison, if maternal varicella precedes delivery long enough to allow transfer of VZV IgG antibodies across the placenta, infants may develop varicella in the first 5 days of life, but it is rarely severe and usually requires no medical intervention.

Zoster occurs only among individuals previously infected with VZV. Zoster used to be common in HIV-infected children who had primary varicella infections when their CD4 counts were normal or mildly

suppressed. In the era before PIs were commonly given to children, among HIV-infected children with low CD4 percentage (i.e., CD4 <15%) at the time of primary varicella, the rate of subsequent zoster was extremely high, about 70% *[950, 951]*. The incidence of zoster among HIV-infected children who had primary varicella when they were immunocompromised was 467 per 1,000 child-years, substantially higher than the 98 per 1,000 person-years observed in immunocompromised HIV-infected adults and the 25 per 1,000 child-years seen among children with leukemia. As in adults, the CD4 count in children correlates with the frequency of zoster recurrences *[962]*. The incidence of zoster is reported to increase transiently after institution of PIs *[22, 963]*. The cause of this phenomenon is not known; one hypothesis is that it is due to return of regulatory T-cell function with transient immune dysregulation. Overall, however, the incidence of herpes zoster in HIV-infected children is lower in the HAART era than it was before it *[3]*. In part, this may also be because many HIV-infected children have been immunized with the Oka vaccine strain.

Clinical Manifestations

Varicella in HIV-infected children may be associated with a prodrome of malaise and fever, followed by the appearance of pruritic vesiculopapular lesions that are more numerous on the face and trunk than on the extremities. Lesions evolve over a 5-day period through macular, papular, vesicular, pustular, and crust stages. In profoundly immunocompromised hosts, vesicles can persist for weeks and coalesce to form large lesions resembling a burn. Complications of varicella include superinfection of skin with bacterial pathogens such as staphylococci and streptococci; neurological manifestations such as encephalitis, cerebellar ataxia, and transverse myelitis; and on occasion vasculitic stroke, hepatitis, and pneumonia.

Initial reports of varicella among HIV-infected children suggested very severe disease manifestations *[964]*, but more recent studies support less complicated courses, particularly in children receiving antiretroviral therapy or with higher CD4 counts at the time of infection *[950, 951, 965, 966]*. However, the duration of disease may be longer than normally seen, and the rate of complications is higher than in otherwise healthy children with varicella *[966]*.

Uncommonly, HIV-infected children may experience persistent chronic infection with continued appearance of new VZV lesions for >1 month after primary or recurrent infection *[967]*. The lesions are characteristically varicelliform at onset but evolve into nonhealing ulcers that become necrotic, crusted, and hyperkeratotic. Persistent lesions may be atypical and lack a vesicular component. Chronic VZV was reported in 14% of HIV-infected children with VZV, usually in children with low CD4 counts *[962]*. The virus may become resistant to acyclovir during prolonged therapy *[968]*.

The classical presentation of zoster is a painful or pruritic unilateral vesicular eruption with a dermatomal distribution. Less typical rashes, however, including those that extend beyond dermatomal boundaries or that are bilaterally distributed or are generalized, may also represent zoster in HIV-infected children. HIV-infected children can have recurrent episodes of reactivated VZV infection that present with a disseminated rash more similar to varicella than zoster but without visceral dissemination; they may also have multiple episodes of recurrent dermatomal disease *[962]*. Encephalitis without rash due to zoster has also been reported *[969]*. Diagnostic laboratory studies should be performed if children or adolescents present with unusual clinical manifestations that are suspected to be due to zoster. It is especially important to rule out HSV infection, which may be confused with VZV skin manifestations *[970]*.

Retinitis is a complication of VZV infection among HIV-infected patients that can be seen in children and adolescents *[971]*. Retinitis due to VZV may be confused with CMV retinitis *[972]*. Progressive outer retinal necrosis is a VZV-associated entity that typically occurs among HIV-infected persons with CD4 counts <50 cells/mm^3. This rapidly progressive necrotizing herpetic retinopathy is often associated with

dermatomal zoster and is characterized by multifocal retinal opacification with little or no ocular inflammation *[973, 974]* and rapid visual loss. Acute retinal necrosis occurs as a peripheral necrotizing retinitis with yellowish thumbprint lesions, retinal vascular sheathing, and vitritis with a high rate of visual loss, often caused by retinal detachment. This latter syndrome can occur in immunologically normal and immunologically deficient persons. Among patients with HIV infection, acute retinal necrosis can occur at any CD4 count, although it more often occurs at higher CD4 counts, and progressive outer retinal necrosis more often occurs at lower CD4 counts.

VZV should be suspected in children with unilateral vesicular rashes, retinitis when CMV cannot be implicated, or with progressive and otherwise unexplained encephalitis and a history of previous varicella or varicella vaccination.

Diagnosis

The diagnosis of varicella and zoster is based clinically on the typical appearance of generalized pruritic vesicular rash and fever in the former and a frequently painful or pruritic unilateral vesicular rash in a dermatomal pattern in the latter. Direct immunofluorescence for VZV antigen can be performed on cells collected from skin, conjunctiva, or mucosal lesion scrapings for diagnosis *[970]*. The optimal sensitivity of this method requires obtaining cells from the base of a lesion after unroofing a fresh vesicle. Direct and indirect immunofluorescence or immunoperoxidase methods also can be used for detection of VZV-infected cells in tissue sections of lung, liver, brain, or other organs. Giemsa-staining (Tzanck preparation) of scrapings from lesions is nonspecific; detection of multinucleated giant cells does not distinguish VZV and HSV infection.

VZV can be isolated in cell culture from vesicular fluid or ulcer swabs, but the virus is very labile. The specimen must undergo rapid processing or be kept on dry ice or frozen at -70°C (-94°F) if storage for more than a few hours is required *[959]*. Five to seven days after inoculation are usually required to detect typical cytopathic effects; confirmation by staining by virus-specific antiserum is then needed. Shell vial cultures combine centrifugation and staining with fluorescein-conjugated monoclonal antibodies to detect synthesis of VZV proteins in infected cells. This allows results 1 to 3 days after inoculation, before cytopathic effect is visible. Standard culture is usually necessary if testing of the virus for antiviral susceptibility is anticipated, although PCR can also be used *[970, 975]*.

PCR can be used to detect VZV in samples, is extremely sensitive and specific, can differentiate between wild-type and vaccine VZV, and is becoming increasingly available and utilized. In some laboratories, PCR has replaced culture as the "gold standard" *[970]*. Serologic tests can be used to diagnose VZV infection, noting a substantial increase in antibody titer during convalescence (e.g., 2 to 3 weeks after onset of illness) or the presence of VZV IgM antibody. VZV reactivation can also induce VZV-IgM antibodies so their presence does not differentiate primary from recurrent VZV infections *[959, 970]*.

Prevention Recommendations

Preventing Exposure

HIV-infected children and adults without evidence of immunity to VZV (with no history of varicella or zoster; or who are seronegative for VZV by a sensitive, specific antibody assay; or who lack evidence of age-appropriate vaccination) should avoid exposure to persons with varicella or zoster **(AII)**. Household contacts of HIV-infected persons without evidence of immunity should receive varicella vaccine if they lack evidence of immunity (i.e., have no history of varicella or zoster, are seronegative for HIV, were born in the United States after 1980, or lack evidence of age-appropriate vaccination) so that they will be less likely to transmit wild-type VZV to their HIV-infected contacts **(AIII)** *[32]*.

Preventing Disease

Varicella

HIV-infected children aged 1 to 8 years in CDC clinical categories N, A, and B and whose CD4 levels are ≥15% should be considered for vaccination (two doses of monovalent single-antigen varicella vaccine); first dose administered at age 12 to 15 months and the second dose 3 months later *[32]* **(BII)**. Limited data from a clinical trial in HIV-infected children with these characteristics indicate that the vaccine was well tolerated and that >80% of subjects had detectable VZV-specific immune response (either antibody or cell immune response or both) at 1 year after immunization *[976, 977]*. Data are not available regarding safety, immunogenicity, or efficacy of MMRV vaccine in HIV-infected children, and MMRV vaccine should not be administered as a substitute for the single-antigen varicella vaccine when vaccinating HIV-infected children.

Data on use of varicella vaccine in older HIV-infected children and adolescents are lacking. However, on the basis of expert opinion, the safety of varicella vaccine in HIV-infected persons aged >8 years with similar levels of immune function (e.g., CD4 count ≥200 cells/mm^3) is likely to be similar to that of children aged <8 years. Immunogenicity might be lower in older HIV-infected children, adolescents, and adults. However, weighing the risk for severe disease from wild-type VZV and potential benefit of vaccination, vaccination (two doses of single-antigen vaccine, administered 3 months apart) for persons with CD4 count ≥200 cells/mm^3 in these age groups may be considered **(BIII)**.

The vaccine is very well tolerated by HIV-infected children; as in healthy children, serious vaccine-related adverse events are rare. As with healthy children, vaccinated HIV-infected children who develop mild rashes >2 weeks after immunization rarely require antiviral therapy for Oka VZV. These rashes usually clear in 3 to 5 days without treatment. If vaccination of HIV-infected persons results in more severe clinical disease, the use of acyclovir to treat the Oka vaccine strain of VZV (which is sensitive to acyclovir) might modify the severity of disease. VZV rashes developing <2 weeks after immunization, however, are usually due to wild-type VZV.

HIV-infected children with low CD4 levels (<15%) may develop pneumonia and neurologic manifestations from VZV and should not be immunized against varicella **(EIII)**. Immunization of such children following reconstitution of their immune system (CD4 percentage ≥15%) with antiretroviral therapy, however, can be considered *[978]*. Zoster from the vaccine (Oka strain) has been reported in healthy children and in children with acute lymphocytic leukemia, but it has not yet been described in HIV-infected children *[979, 980]*.

As yet, efficacy studies on prevention of varicella in HIV-infected children are not available. The effectiveness of varicella vaccine in immunized healthy children (after one dose) and those with underlying leukemia (after two doses) is about 80% – 85% prevention of clinical infection, with modified varicella in most of the remainder *[949]*.

For post-exposure prophylaxis against varicella, HIV-infected children and adolescents who lack evidence of immunity to VZV (i.e., with no history of varicella or zoster; or who are seronegative for VZV by a sensitive, specific antibody assay; or who lack evidence of age-appropriate vaccination) should be passively immunized as soon as possible and in <96 hours after close contact with a person with varicella or zoster **(AIII)**. Previously this was performed by administering varicella-zoster immune globulin (VZIG). Licensure of varicella vaccine in the United States has resulted in dramatically fewer requests for VZIG; therefore, VZIG is no longer being produced. A new product, human varicella immune globulin (VariZIG), manufactured in Canada, is the replacement. VariZIG is a lyophilized presentation which, when properly reconstituted, is approximately a 5% solution of IgG that can be

administered intramuscularly. VariZIG is available under an investigational new drug application expanded access protocol (available at **http://www.fda.gov/cber/infosheets/mphvzig020806.htm**) *[981]*. VariZIG can be obtained in the United States, and it has received central institutional review board (IRB) approval, but local IRB approval may also be necessary. VariZIG can be obtained 24 hours a day from the sole authorized U.S. distributor (FFF Enterprises, Temecula, California) at 1-800-843-7477 or online at **http://www.fffenterprises.com**. An alternative to VariZIG for passive immunization is IVIG 400 mg/kg, administered once. IVIG should also be administered within 96 hours of exposure.

Data are lacking regarding the effectiveness of acyclovir for preventing varicella among susceptible HIV-infected children. There is minimal published information on this form of prophylaxis for healthy children *[982-984]*. If VariZIG is not available or >96 hours have passed since exposure, some experts recommend prophylaxis with acyclovir (80 mg/kg/day, administered four times per day for 5 to 7 days; beginning from Day 7 to Day 10 after exposure, maximum dose of 80 mg, four times per day) *[90]*. However, the use of acyclovir for prophylaxis in HIV-infected VZV-exposed children has not been studied. For that reason, some experts would consider it prudent to wait until the first appearance of rash to start acyclovir therapy for the VZV-susceptible and -exposed HIV-infected child to whom passive immunization was not given **(CIII)**.

Treatment Recommendations

Treatment of Disease

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)**. For 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 to 7 days. Intravenous acyclovir is recommended for treatment of primary varicella among HIV-infected children with severe immunosuppression (i.e., CD4 <15%, CDC Immunolgic Category 3) *[985]* 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/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/meter^2 body surface area/dose intravenously every 8 hours as a 1-hour infusion) *[90]*. Administration is for 7 to 10 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 counts (CDC Immunologic Category 1 or 2) *[985]* who have mild varicella disease **(BIII)**.

Acyclovir is the treatment of choice for zoster among HIV-infected children, administered for 7 to 10 days, although longer durations of therapy should be considered if lesions are slow to resolve **(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 (i.e., CD4 <15%, CDC Immunologic Category 3) *[985]*, trigeminal nerve involvement, or extensive multidermatomal zoster **(AII)**. If cutaneous lesions are extensive or if clinical evidence of visceral involvement is observed, intravenous acyclovir should be initiated and continued until cutaneous lesions and visceral disease are clearly resolving **(AII)**, then change to oral administration can be considered to complete the course of therapy (10 to 14 days in this situation) **(AIII)** *[986]*. Doses of acyclovir for the treatment of zoster are the same as those for varicella.

Progressive outer retinal necrosis is rapidly progressive and leads to profound loss of vision; prognosis for visual preservation is poor despite aggressive therapy and optimal therapy is yet to be defined *[987, 988]*. Regardless of specific VZV antiviral therapy, optimization of antiretroviral therapy is also recommended. Some experts recommend anti-VZV therapy that includes a combination of intravenous ganciclovir (5

mg/kg/dose given intravenously every 12 hours) and foscarnet (90 mg/kg/dose given intravenously every 12 hours) plus twice-weekly intravitreal injections of ganciclovir (2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL) *[989]* **(BIII)**. In contrast, acute retinal necrosis appears more responsive to antiviral therapy, and one recommended treatment is high-dose intravenous acyclovir (10 – 15 mg/kg intravenously every 8 hours for 10 to 14 days), followed by prolonged (i.e., 4 to 6 weeks) oral valacyclovir *[989]* **(AIII)**. Involvement of an ophthalmologist experienced with management of patients with VZV retinitis is strongly recommended **(AIII)**.

Alternatives to acyclovir in older adolescents and adults include valacyclovir and famciclovir. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption and is approved for treatment of zoster in adults. It is not active against acyclovir-resistant VZV strains. Data are limited for its use in children *[862, 990]*; bioavailability is about 45% and independent of age in children. Based on limited available data, pediatric blood levels of acyclovir (from the prodrug valacyclovir) similar to that of valacyclovir tablets in adults can be achieved by administering an oral dose of valacyclovir of 20 – 25 mg/kg/dose given two or three times a day *[863]* **(CIII)**. However, valacyclovir is available only in a caplet formulation, and hence this drug is an alternative only for children old enough to swallow the valacyclovir caplets. Although tablets can be crushed, they have a very unpleasant taste. A liquid formulation that is stable for 21 days can be prepared in Ora-Sweet and Syrpalta syrups and stored in amber glass bottles *[990]*.

Famciclovir is the oral prodrug of penciclovir. It is not active against acyclovir-resistant VZV strains. 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. There are no specific data on the pharmacokinetics and dosing of famciclovir in children and no pediatric preparation is available *[863]*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

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. Toxicities are similar for valacyclovir. 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 *[856]*. Grade 3 or higher nephrotoxicity was observed in 6% of children. For children receiving high-dose IV acyclovir, monitoring of renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction or those receiving prolonged therapy.

In HIV-infected adults, immune reconstitution following initiation of HAART may be associated with an increased frequency of VZV reactivation *[963, 991]*. VZV-associated IRIS following HAART has also been described in HIV-infected children *[20, 24]*. In a study in 153 HAART-treated children in Thailand, 19% of children starting HAART experienced IRIS; 22% of the cases of IRIS were secondary to VZV. In the reported cases, manifestations were cutaneous and generally mild, manifested as VZV reactivation in a typical dermatomal distribution of vesicular lesions, and responded well to treatment with oral acyclovir. Most cases present in the first 4 months of HAART; the median time from the initiation of HAART to the onset of clinical symptoms in the Thai children was 6 weeks (range: 2 to 21 weeks) *[24]*.

Management of Treatment Failure

Children who continue to develop lesions or whose lesions fail to heal after 10 days of treatment may be infected with acyclovir-resistant VZV. If possible, a culture should be obtained to analyze the virus for drug resistance. HIV-infected children with acyclovir-resistant VZV can be treated with intravenous foscarnet for 7 days or until no new lesions have appeared for 48 hours *[989, 992, 993]* **(AII)**. 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; ≤30% of patients experience an increase in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions (e.g., calcium) lead 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.

Prevention of Recurrence

Preventing Recurrence

Zoster

No preventive measures are available for zoster in HIV-infected children and adolescents. A vaccine for prevention of herpes zoster has been approved for use in immunocompetent adults >60 years of age. Data regarding safety and efficacy of this vaccine in HIV-infected individuals of any age are lacking and its use in HIV-infected individuals is not recommended at the present time **(DIII)**. However, prospective clinical trials to evaluate the safety and immunogenicity of herpes zoster vaccine in HIV-infected adults are planned.

Discontinuing Secondary Prophylaxis

Not applicable.

TABLE 1. Prophylaxis to Prevent First Episode of Opportunistic Disease Among HIV-Exposed and HIV-Infected Infants and Children

Pathogen	Preventive regimen		
	Indication	First choice	Alternative
I. Strongly recommended as standard of care			
Pneumocystis pneumonia (PCP)*	HIV-infected or HIV- indeterminate infants aged 1 to 12 mos; HIV-infected children aged 1 to 5 yrs with CD4 count <500 cells/mm^3 or CD4 percentage <15%; HIV-infected children aged 6 to 12 yrs with CD4 count <200 cells/mm^3 or CD4 percentage <15%	• Trimethoprim-sulfamethoxazole (TMP-SMX), 150/750mg/m^2 body surface area per day daily divided into 2 doses and given 3 times weekly on consecutive days **(AI)**; • Acceptable alternative dosage schedules for same dosage **(AI)**: single dose by mouth 3 times weekly on consecutive days; 2 divided doses by mouth given daily; or 2 divided doses by mouth 3 times weekly on alternate days	• Dapsone (children aged ≥1 mos), 2mg/kg body weight (max 100mg) by mouth daily or 4mg/kg body weight (max 200mg) by mouth weekly **(BI)** • Atovaquone (children aged 1 to 3 mos and >24 mos, 30mg/kg body weight by mouth daily; children aged 4 to 24 mos, 45 mg/kg body weight by mouth daily) **(BI)** • Aerosolized pentamidine (children aged ≥5 yrs), 300mg every month via Respirgard II™ (manufactured by Marquest, Englewood, Colorado) nebulizer **(BI)**
Malaria	Travel to endemic area	• Recommendations are the same for HIV-infected and -uninfected children. Please refer to the following website for the most recent recommendations based on region and drug susceptibility: **http://www.cdc.gov/malaria/** • Mefloquine 5mg/kg body weight orally given once weekly (max 250mg) • Atovaquone/Proguanil (Malarone) once daily 11–20 kg = 1 Pediatric Tablet (62.5mg/25mg) 21–30 kg = 2 Pediatric Tablets (125mg/50mg) 31–40 kg = 3 Pediatric Tablets (187.5mg/75mg) >40 kg = 1 Adult Tablet (250mg/100mg)	• Doxycycline 100mg by mouth daily for children >8 years (2.2mg/kg//day). • Chloroquine base: 5mg/kg base PO, up to 300mg weekly FOR sensitive regions only (7.5mg/kg chloroquine phosphate)
Mycobacterium tuberculosis:			
• Isoniazid-sensitive	Tuberculin skin test (TST) reaction, ≥5 mm or prior positive TST result without treatment; or regardless of current TST result and previous treatment, close contact with any person with contagious TB. TB disease must be excluded before starting treatment.	• Isoniazid, 10–15mg/kg body weight (max 300mg) by mouth daily for 9 mos **(AII);** or 20–30mg/kg body weight (max 900mg) by mouth twice weekly for 9 months **(BII)**	• Rifampin, 10–20mg/kg body weight (max 600mg) by mouth daily for 4 to 6 mos **(BIII)**
• Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	• Rifampin, 10–20mg/kg body weight (max 600mg) by mouth daily for 4 to 6 mos **(BIII)**	• Uncertain
• Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	• Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	

TABLE 1. Prophylaxis to Prevent First Episode of Opportunistic Disease Among HIV-Exposed and HIV-Infected Infants and Children (Continued)

Pathogen	Preventive regimen		
	Indication	**First choice**	**Alternative**
Mycobacterium avium complex†	For children aged ≥6 yrs with CD4 count <50 cells/mm^3; aged 2 to 5 yrs with CD4 count <75 cells/mm^3; aged 1 to 2 yrs with CD4 count <500 cells/mm^3; aged <1 yr with CD4 count <750 cells/mm^3	• Clarithromycin, 7.5mg/kg body weight (max 500mg) by mouth twice daily **(AII)**; or azithromycin, 20mg/kg body weight (max 1,200mg) by mouth weekly **(AII)**	• Azithromycin, 5mg/kg body weight (max 250mg) by mouth daily **(AII)**; children aged ≥6 yrs, rifabutin, 300mg by mouth daily **(BI)**
Varicella-zoster virus§	Substantial exposure to varicella or shingles with no history of varicella or zoster or who are seronegative for VZV by a sensitive, specific antibody assay or who lack evidence of age appropriate vaccination	• Varicella-zoster immune globulin (VariZIG) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hours after exposure **(AIII)** Note: As of 2007, VariZIG can be obtained only under a treatment IND (1-800-843-7477, FFF Enterprises)	• If VariZIG is not available or >96 hours have passed since exposures, some experts recommend prophylaxis with acylovir 20mg/kg body weight (max 800mg) pre-dose by mouth 4 times a day for 5 to 7 days. Another alternative to VariZIG is intravenous immune globulin (IVIG) 400mg/kg, administered once. IVIG should be administered within 96 hours of exposure **(CIII)**.
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed/infected children	• Routine immunizations (see Figures 1 and 2)	
II. Usually recommended			
*Toxoplasma gondii***	Immunoglobulin G (IgG) antibody to *Toxoplasma* and severe immunosuppression: HIV-infected children aged <6 years with CD4 percentage <15%; HIV-infected children aged >6 years with CD4 count <100 cells/mm^3 **(BIII)**	• TMP-SMX, 150/750mg/m^2 body surface area daily by mouth in 2 divided doses **(BIII)** • Acceptable alternative dosage schedules for same dosage **(AI)**: single dose by mouth 3 times weekly on consecutive days; 2 divided doses by mouth given daily; or 2 divided doses by mouth 3 times weekly on alternate days	• Dapsone (children aged ≥1 mos), 2mg/kg body weight or 15mg/m^2 body surface area (max 25mg) by mouth daily PLUS pyrimethamine, 1mg/kg body weight (max 25mg) by mouth daily PLUS leucovorin, 5mg by mouth every 3 days **(BI)** • Atovaquone (children aged 1 to 3 mos and >24 mos, 30mg/kg body weight by mouth daily; children aged 4 to 24 mos, 45mg/kg body weight by mouth daily) with or without pyrimethamine, 1mg/kg body weight or 15mg/m^2 body surface area (max 25mg) by mouth daily PLUS leucovorin, 5mg by mouth every 3 days **(CIII)**
III. Not recommended for the majority of children; indicated for use only in unusual circumstances			
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400mg/dL)	• Intravenous immune globulin (400mg/kg body weight every 2 to 4 weeks) **(AI)**	
Cytomegalovirus (CMV)	CMV antibody positivity and severe immunosuppression (CD4 count <50 cells/mm^3)	• Valganciclovir 900mg by mouth once daily with food for older children who can receive adult dosing **(CI)**	

Notes: Information included in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for products or indications. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval. Letters and Roman numerals in parentheses after regimens indicate the strength of the recommendation and the quality of the evidence supporting it (see Box).

* Daily TMP-SMX reduces the frequency of certain bacterial infections. TMP-SMX, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis, although data have not been prospectively collected. When compared with weekly dapsone, daily dapsone is associated with lower incidence of *Pneumocystis* pneumonia (PCP) but higher hematologic toxicity and mortality *[994]*. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMX.

† Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and non-nucleoside reverse transcriptase inhibitors. A specialist should be consulted.

§ Children routinely being administered intravenous immune globulin (IVIG) should receive VariZIG if the last dose of IVIG was administered >21 days before exposure.

**Protection against toxoplasmosis is provided by the preferred anti-pneumocystis regimens and possibly by atovaquone.

TABLE 2. Prophylaxis to Prevent Recurrence of Opportunistic Disease, After Chemotherapy for Acute Disease, among HIV-Infected Infants and Children

Pathogen	Preventive regimen: Indication	First choice	Alternative
I. Recommended as standard of care following completion of initial therapy			
Pneumocystis pneumonia (PCP)*	Prior *Pneumocystis* pneumonia (PCP)	• Trimethoprim-sulfamethoxazole (TMP-SMX), 150/750mg/m^2 body surface area daily by mouth divided into 2 doses and given 3 times weekly on consecutive days **(AI)** • Acceptable alternative dosage schedules for same dosage: **(Al)** single dose by mouth 3 times weekly on consecutive days; 2 divided doses by mouth given daily; or 2 divided doses by mouth 3 times weekly on alternate days	• Dapsone (children aged ≥1 mos), 2mg/kg body weight (max 100mg) by mouth daily or 4mg/kg body weight (max 200mg) by mouth weekly **(BI)**; • Atovaquone (children aged 1 to 3 mos and >24 mos, 30mg/kg body weight by mouth daily; children aged 4 to 24 mos, 45mg/kg body weight by mouth daily) **(BI)** • Aerosolized pentamidine (children aged ≥5 yrs), 300mg every month via Respirgard II™ (manufactured by Marquest, Englewood, Colorado) nebulizer **(BI)**
*Toxoplasma gondii**	Prior toxoplasmic encephalitis	• Sulfadiazine, 85–120mg/kg body weight (max 2–4 grams) daily by mouth divided into in 2–4 doses PLUS pyrimethamine, 1mg/kg body weight or 15mg/m^2 body surface area (max 25mg) by mouth daily PLUS leucovorin, 5mg by mouth every 3 days **(AI)**	• Clindamycin, 20–30mg/kg body weight daily by mouth divided into 3–4 doses PLUS pyrimethamine, 1mg/kg body weight or 15mg/m^2 body surface area (max 25mg) by mouth daily PLUS leucovorin, 5mg by mouth every 3 days **(BI)** • Atovaquone (children aged 1 to 3 mos and >24 mos, 30mg/kg body weight by mouth daily; children aged 4 to 24 mos, 45mg/kg body weight by mouth daily) with or without pyrimethamine, 1mg/kg body weight or 15mg/m^2 body surface area (max 25mg) by mouth daily PLUS leucovorin, 5mg by mouth every 3 days **(CIII)**
Mycobacterium avium complex†	Prior disease	• Clarithromycin, 7.5mg/kg body weight (max 500mg) by mouth twice daily **(AII)** PLUS ethambutol, 15–25mg/kg body weight (max 2.5grams) by mouth daily **(AII)**; with or without rifabutin, 5mg/kg body weight (max 300mg) by mouth daily **(CII)**	• Azithromycin, 5 mg/kg body weight (max 250 mg) by mouth daily **(AII)** PLUS ethambutol, 15–25 mg/kg body weight (max 2.5 grams) by mouth daily **(AII)**; with or without rifabutin, 5 mg/kg body weight (max 300 mg) by mouth daily **(CII)**
Coccidioides spp. (not routinely recommended)	Documented disease	• Fluconazole, 6mg/kg body weight (max 400mg) by mouth daily **(AII)**	• Itraconazole, 2–5mg/kg body weight (max 200mg) by mouth per dose twice daily **(AII)**
Cryptococcus neoformans	Documented disease	• Fluconazole, 6mg/kg body weight (max 200mg) by mouth daily **(AI)**	• Itraconazole oral solution, 5mg/kg body weight (max 200mg) by mouth daily **(BI)**
Histoplasma capsulatum	Documented disease	• Itraconazole oral solution, 5mg/kg body weight (max 200mg) by mouth per dose twice daily **(AII)**	• Fluconazole, 3–6mg/kg body weight (max 200mg) by mouth daily **(CII)**
Microsporidiosis	Disseminated, non-ocular infection caused by microsporidia other than *Enterocytozoon bieneusi*	• Albendzaole 7.5mg/kg body weight (max 400mg/dose) per dose by mouth twice daily **(AII)** until immune reconstitution after initiation of HAART	
	Ocular infection	• Topical fumagillin bicylohexylammonium (Fumidil B) 3mg/mL in saline (fumagillin 70μg/ml) eye drops - 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **(BII)** PLUS albendazole 7.5mg/kg body weight (max 400mg/dose) by mouth twice daily for management of systemic infection **(BIII)**	

TABLE 2. Prophylaxis to Prevent Recurrence of Opportunistic Disease, After Chemotherapy for Acute Disease, among HIV-Infected Infants and Children (Continued)

	Preventive regimen		
Pathogen	**Indication**	**First choice**	**Alternative**
Cytomegalovirus	Prior retinitis, neurologic disease, or gastrointestinal disease with relapse	• Ganciclovir, 5 mg/kg body weight intravenously daily **(AI);** or • Foscarnet, 90–120 mg/kg body weight intravenously daily **(AI);** or • Valganciclovir 900 mg by mouth once daily with food for older children who can receive adult dosing **(AI)**	• (For retinitis) Ganciclovir sustained release implant, every 6 to 9 mos plus ganciclovir, 30 mg/kg body weight by mouth 3 times daily **(BIII)**
II. Recommended only if subsequent episodes are frequent or severe			
Invasive bacterial Infections¶	>2 infections in a 1-year period	• TMP-SMX, 150/750 mg/m^2 body surface area daily by mouth divided into in 2 doses **(BI)** • Intravenous immune globulin (IVIG), 400 mg/kg body weight every 2 to 4 weeks **(AI)**	• Antibiotic chemoprophylaxis with another active agent **(BIII)**
Bartonellosis	Frequent or severe recurrences	• Doxycycline 2–4 mg/kg body weight (max 100–200 mg/day) per day by mouth given once daily or divided into 2 doses **(AIII)**	• One of the macrolide antibiotics **(AIII)** (e.g., azithromycin 5–12 mg/kg body weight (max 600 mg/day) by mouth once daily; clarithromycin 15 mg/kg body weight (max 1 gram/day) per day by mouth divided into 2 doses; or erythromycin 30–50 mg/kg body weight (max 2 grams/day) per day by mouth divided into 2 doses **(AIII)**
Candida (esophageal)	Frequent or severe recurrences	• Fluconazole, 3–6 mg/kg body weight (max 200 mg) by mouth daily **(BI)**	
Herpes simplex virus	Frequent or severe recurrences	• Acyclovir 20 mg/kg body weight (max 400 mg/dose) per dose by mouth twice daily **(AI)**	• Valacyclovir 500 mg by mouth twice daily or famicilovir 500 mg by mouth twice daily for children old enough to receive adult dosing **(AI)**

Notes: Information included in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for products or indications. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval. Letters and Roman numerals in parentheses after regimens indicate the strength of the recommendations and the quality of evidence supporting it (see Box).

* Pyrimethamine plus sulfadiazine, and possibly atovaquone, confers protection against PCP as well as toxoplasmosis. Although the clindamycin plus pyrimethamine or atovaquone with or without pyrimethamine regimens are recommended for adults, they have not been tested among children. However, these drugs are safe and are used for other infections in children.

† Substantial drug interactions might occur between rifabutin and protease inhibitors and non-nucleoside reverse transcriptase inhibitors. A specialist should be consulted.

¶ Antimicrobial prophylaxis should be chosen on the basis of microorganism and antibiotic sensitivities. TMP-SMX, if used, should be administered daily. Health-care providers should be cautious regarding using antibiotics solely for this purpose because of the potential for development of drug-resistant microorganisms. IVIG might not provide additional benefit to children receiving daily TMP-SMX but might be considered for children who have recurrent bacterial infections despite TMP-SMX prophylaxis. Choice of antibiotic prophylaxis versus IVIG should also involve consideration of adherence, ease of intravenous access, and cost. If IVIG is used, respiratory syncytial virus (RSV) IVIG (750mg/kg body weight), not monoclonal RSV antibody, can be substituted for IVIG during the RSV season to provide broad anti-infective protection, if this product is available.

TABLE 3. Criteria for Discontinuing and Restarting Opportunistic Infection Prophylaxis for HIV-Infected Children

Opportunistic Illness	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis	Criteria for discontinuing secondary prophylaxis	Criteria for restarting secondary prophylaxis
Pneumocystis Pneumonia (PCP)	• Do not discontinue in children aged <1 year • After ≥6 months of HAART and: • Age 1 to 5 years, CD4 percentage or count is ≥15% or ≥500 cells/mm^3 for >3 consecutive months **(BII)** • Age ≥6 years, CD4 percentage or count is ≥15% or ≥200 cells/mm^3 for >3 consecutive months **(BII)**	• Age 1 to 5 years with CD4 percentage <15% or count <500 cells/mm^3 **(BIII)** • Age ≥6 years with CD4 percentage <15% or count <200 cells/mm^3 **(BIII)**	If fulfill all of the following criteria **(CIII)**: • Completed ≥6 months of HAART • Age 1 to 5 years, CD4 percentage or count is ≥15% or ≥500 cells/mm^3 for >3 consecutive months **(BII)** • Age ≥6 years, CD4 percentage or count is ≥15% or ≥200 cells/mm^3 for >3 consecutive months **(BII)**	• Age 1 to 5 years with CD4 percentage <15% or count <500 cells/mm^3 or recurrence PCP **(BIII)** • Age ≥6 years with CD4 percentage <15% or CD4 count <200 cells/mm^3 or recurrence PCP **(BIII)**
Toxoplasma gondii Encephalitis (TE)	• Do not discontinue in children aged <1 year • After ≥6 months of HAART and: • Age 1 to 5 years, CD4 percentage is ≥15% for >3 consecutive months **(CIII)** • Age ≥6 years, CD4 percentage or count is ≥15% or >100–200 cells/mm^3 for >3 consecutive months **(CIII)**	• Age 1 to 5 years with CD4 percentage <15% **(CIII)** • Age ≥6 years with CD4 percentage <15% or CD4 count <100–200 cells/mm^3 **(CIII)**	If fulfill all of the following criteria **(CIII)**: • Completed ≥6 months of HAART • Completed initial therapy for TE • Asymptomatic for TE • Age 1–5 years, CD4percentage is ≥15% for >3 consecutive mos **(CIII)** • Age ≥6 years, CD4 percentage or count is ≥15% or >200 cells/mm^3 for >3 consecutive months **(CIII)**	• Age 1 to 5 years with CD4 percentage <15% **(CIII)** • Age ≥6 years with CD4 percentage <15% or CD4 count <200 cells/mm^3 **(CIII)**
Mycobacterium avium complex (MAC) disease	• Do not discontinue in children aged <2 years. • If age >2 years, after ≥6 months of HAART and: • Age 2 to 5 years with CD4 count >200 cells/mm^3 for >3 consecutive months **(BII)** • Age ≥6 years with CD4 count >100 cells/mm^3 for >3 consecutive months **(BII)**	• Age 2 to 5 years with CD4 count <200 cells/mm^3 **(BIII)** • Age ≥6 years with CD4 count <100 cells/mm^3 **(BIII)**	If fulfill all of the following criteria **(CIII)**: • Completed ≥6 months of HAART • Completed at least 12 months MAC therapy • Asymptomatic for signs and symptoms of MAC • Age 2 to 5 years with CD4 count >200 cells/mm^3 for ≥6 consecutive months **(BII)** • Age ≥6 years with CD4 count >100 cells/mm^3 for ≥6 consecutive months **(BII)**	• Age 2 to 5 years with CD4 count <200 cells/mm^3 **(BII)** • Age ≥6 years with CD4 count <100 cells/mm^3 **(BII)**
Cytomegalovirus retinitis	• Not applicable	• Not applicable	If fulfill all of the following criteria **(CIII)**: • Completed ≥6 months of HAART. • Consultation with ophthalmologist • Age 1 to 6 years with CD4 percentage ≥15% or CD4 count >500 cells/mm^3 for >3 consecutive months • Age >6 years with CD4 count >100 cells/mm^3 for >3 consecutive months Routine (every 3 to 6 month) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis **(AII)**	• Age 1 to 6 years with CD4 percentage <15% or count <500 cells/mm^3 **(CIII)** • Age >6 years with CD4 count <100 cells/mm^3 or CD4 percentage <15% **(CIII)**
Cryptococcal meningitis	• Not applicable	• Not applicable	If fulfill all of the following criteria **(BII)**: • Asymptomatic on ≥6 months of secondary prophylaxis for crypotoccosis • Completed ≥6 months of HAART • Age >6 years with CD4 count ≥200 cells/mm^3 for >6 months	• CD4 count <200/mm^3 **(AIII)**
Histoplasma capsulatum infection	• Not applicable	• Not applicable	If fulfill all of the following criteria **(CIII):** • Age >6 years • Received ≥1 year itraconazole • Completed ≥6 months of HAART • CD4 count >150 cells/mm^3 and percentage ≥15% • Negative *Histoplasma* blood cultures • Serum *Histoplasma* antigen <2 ng/mL	• CD4 count <150 cells/mm^3 or percentage <15% **(CIII)**

TABLE 4. Recommendations for Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Infants and Children*

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
BACTERIAL INFECTIONS			
Bacterial pneumonia *(S. pneumoniae;* occasionally *S. aureus, H. influenzae, P.* aeruginosa*)*	• Ceftriaxone 80–100mg/kg body weight per day (max 4 grams/day) in 1 or 2 divided doses OR • Cefotaxime 150–200mg/kg body weight (max 8–10 grams/day) per day divided into 3 or 4 doses	• Cefuroxime 100–150mg/kg body weight (max 4–6 grams/day) divided into 3 doses	• Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (*Mycoplasma pneumoniae, C. pneumoniae*) • Add clindamycin or vancomycin if methicillin-resistant *S. aureus* suspected (choice based on local susceptibility patterns) • For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (e.g., cefepime instead of ceftriaxone) • Consider PCP in patients with severe pneumonia or more advanced HIV disease • Consider evaluation for tuberculosis and cryptococcosis
Bartonellosis	*Cutaneous **bacillary** angiomatosis infections:* • Erythromycin 30–50 mg/kg body weight (max 2 grams/day) per day by mouth divided into 2–4 doses, or if unable to take oral medication, 15–50 mg/kg body weight (max 2 grams/day) per day intravenously (IV) in divided doses 4 times a day **(AII)** • Doxycycline 2–4 mg/kg body weight (max 100–200mg/day) per day by mouth or IV given once daily or divided into 2 doses **(AII)** ***Treatment duration:*** 3 months ***CNS infections, peliosis hepatis, osteomyelitis, and severe infections:*** • Doxycycline 2–4mg/kg body weight (max 100–200mg/day) per day by mouth or IV given once daily or divided into 2 doses **(AIII)** ***Treatment** duration:* 4 months	• Rifampin 20mg/kg body weight (max 600mg/day) per day by mouth or IV given once daily or divided into 2 doses can be used in combination with erythromycin or doxycycline in patients with more severe infections **(BIII)** • Azithromycin 5–12mg/kg body weight (max 600mg/day) by mouth once daily **(BII)** • Clarithromycin 15mg/kg body weight (max 1 gram/day) per day by mouth divided into 2 doses **(BII)**	• Severe Jarisch-Herxheimer-like reaction can occur in the first 48 hours of treatment • Long-term suppression with erythromycin or doxycycline may be considered in patients with relapse or reinfection **(CIII)**

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Syphilis	*Congenital:* ***Proven or Highly Probable Disease:*** • Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight IV every 12 hours for the first 7 days of life then every 8 hours for a total of 10 days **(AII)** • If diagnosed after 1 month of age, aqueous penicillin G 200,000–300,000 unit/kg body weight, administered as 50,000 units/kg body weight IV every 4 to 6 hours (max 18–24 million units per day) for 10 days **(AII)** ***Acquired:*** ***Early Stage (primary, secondary, early latent):*** • Benzathine penicillin 50,000 units/kg body weight (max 2.4 million units) intramuscularly (IM) for 1 dose **(AII)** ***Late Latent:*** • Benzathine penicillin 50,000 units/kg body weight (max 2.4 million units) IM once weekly for 3 doses **(AIII)** ***Neurosyphilis (including ocular):*** • Aqueous penicillin G 200,000–300,000 units/kg body weight per day IV in divided doses given every 4 to 6 hours (max 18–24 million units per day) for 10 to 14 days **(AII)**	*Congenital:* ***Alternative for Proven or Highly Probable Disease (less desirable if central nervous system involvement):*** • Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days **(BII)** ***Infants with Possible Congenital Syphilis (maternal treatment and response adequate, normal physical examination, normal cerebrospinal fluid studies, but serum quantitative non-treponemal serologic titer that is the same or 4-fold higher than maternal titer):*** • Benzathine penicillin G 50,000 units/kg body weight IM in a single dose (max 2.4 million units) **(BII)**	• For treatment of congenital syphilis, repeat entire course of treatment if even 1 day of treatment is missed • Children with congenital syphilis should be evaluated at 1, 2, 3, 6, and 12 months of age, and have nontreponemal testing at 3, 6, and 12 months after conclusion of therapy or until test becomes negative **(AIII)**. Children with increasing titers or persistently positive titers (even if low levels) at age 6 to 12 months should be evaluated and considered for retreatment **(AIII)**. • Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy **(BIII)**

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
MYCOBACTERIAL INFECTIONS			
Mycobacterium tuberculosis (TB)	***Intensive** Phase **(8 weeks)** **(AI)**:* • Isoniazid 10–15mg/kg body weight (max 300mg/day) by mouth once daily PLUS rifampin 10–20mg/kg body weight (max 600mg/day) by mouth once daily PLUS pyrazinamide 20–40mg/kg (max 2 gm/day) body weight by mouth once daily PLUS ethambutol 15–25mg/kg body weight (max 2.5 gm/day) by mouth once daily **(AI)** ***Continuation** phase **(for drug- susceptible TB)** **(AI)**:* ***Daily:*** • Isoniazid 10–15mg/kg body weight (max 300mg/day) by mouth once daily PLUS rifampin 10–20mg/kg body weight (max 600mg/day) by mouth once daily **(AII)** ***Intermittent:*** • Isoniazid 20–30mg/kg body weight (max 900mg/day) by mouth once daily given 3 times a week PLUS rifampin 10–20mg/kg body weight (max 600mg/day) by mouth once daily given 3 times a week **(AI)**; administration of the drugs twice a week may be considered only for children who are not immune suppressed (i.e., CD4 >15% or >100 cells/mm^3 if >6 years) **(CIII)** ***Treatment** duration **(drug-sensitive TB)** **(AIII)**:* • ***Pulmonary TB:*** 9 months for HIV-infected child (6 months if not HIV-infected) • ***Extrapulmonary TB:*** 12 months	• Alternative drug for rifampin is rifabutin 10–20mg/kg body weight (max 300mg/day) by mouth once daily (same dose is given for intermittent 2 or 3 times weekly regimen) **(BIII)** • Alternative drug for ethambutol is streptomycin 20–40mg/kg body weight (max 1 gm/day) IM once daily (or 20mg/kg given as intermittent 2 or 3 times weekly regimen) **(BIII)** • Ethionamide 15–20mg/kg body weight by mouth (max 1 gm/day) divided into 2 or 3 doses per day should be used for tuberculosis meningitis **(AIII)** ***Drug-Resistant TB:*** ***Resistance to isoniazid alone:*** • Discontinue isoniazid • Rifampin PLUS pyrazinamide PLUS ethambutol (ethionamide or streptomycin can be substituted for ethambutol if *M. tuberculosis* isolate is susceptible to these agents) **(BII)** ***Resistance to rifampin alone:*** • Discontinue rifampin • Isoniazid PLUS pyrazinamide PLUS ethambutol PLUS streptomycin for first 2 months, followed by continuation phase of isoniazid PLUS pyrazinamide PLUS ethambutol to complete 12 to 18 month course **(BIII)** • For older adolescents: isoniazid PLUS pyrazinamide PLUS ethambutol PLUS a fluoroquinolone for 2 months, followed by isoniazid PLUS ethambutol PLUS a fluoroquinolone to complete 12 to 18 month course (**BIII**) ***Multi-drug resistance:*** • Therapy should be based on resistance pattern (of child or of source case where child's isolate is not available) and children should be managed in consultation with an expert consultant **(AIII)** ***Treatment duration (drug-resistant TB)** **(AIII)**:* • ***Single drug INH resistant TB:*** 9 to 12 months **(BII)**	• Directly observed therapy should be standard of care for children with TB **(AII)** • Potential drug interactions should be carefully reviewed • In antiretroviral-naïve child, initiate therapy for TB 2 to 8 weeks prior to starting antiretroviral drugs **(BII)**; for children already receiving antiretroviral therapy who are diagnosed with TB, 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 **(AIII)** • For children with severe immunosuppression (CD4 <15% or if over age 6 yrs, <100 cells/mm^3), continuation phase for drug-susceptible TB disease should include either daily or thrice-weekly treatment; twice-weekly regimens should *not* be used because they may lead to rifamycin resistance in immunosuppressed patients **(AII)** • Pyroxidine should be given if isoniazid or cycloserine is administered **(AII)** • Adjunctive treatment with corticosteroids is indicated for children with central nervous system disease **(AII)**, and may be considered for children with pleural or pericardial effusions, severe miliary disease, and significant endobronchial disease **(BIII)** • Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination **(AIII)** • Thiacetazone can cause severe or fatal reactions in HIV-infected children including rash and aplastic anemia and should not be used **(EIII)** • For drug resistant strains, ≥2 drugs to which the isolate is susceptible should be given (minimum of 3 drugs should be given through the continuation phase of therapy) ***For Multi-Drug-Resistant TB, Second-Line Drugs Include:*** • Amikacin 15–30mg/kg body weight (max 1 gm/day) IM once daily • Capreomycin 15–30mg/kg body weight (max 1 gm/day) IM once daily • Ciprofloxacin 10–15mg/kg body weight by mouth twice daily (max 1.5 gm/day); levofloxicin 500–1000mg by mouth once daily; or moxifloxacin 400mg by mouth once daily (fluoroquinolones are not labeled for use in children <18 years old due to concerns regarding potential effects on cartilage; use in younger persons requires an assessment of potential risks and

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Mycobacterium tuberculosis (TB) (con't)		• ***Single drug rifampin resistant TB:*** 12 to 18 months **(BIII)** • ***Multi-drug resistant TB:*** 18 to 24 months after culture conversion in children with bacteriologic confirmation; ≥12 months in children who were culture-negative at treatment initiation	benefits) **(CIII)** • Cycloserine 10–20mg/kg body weight (max 1 gm/day) by mouth once daily • Ethionamide/prothionamide 15–20mg/kg body weight (max 1 gm/day) by mouth in 2–3 divided doses • Kanamycin 15–30mg/kg body weight (max 1 gm/day) IM once daily • Para-aminosalicylic acid 200–300mg/kg body weight by mouth divided into 3–4 doses per day (max 10 gm/day) • Streptomycin 20–40mg/kg body weight (max 1 gm/day) IM once daily
Mycobacterium avium Complex (MAC)	***Initial** Treatment **(≥2 drugs):*** **(AI)** • Clarithromycin 7.5–15mg/kg body weight (max 500mg/dose) by mouth twice daily **(AI)** PLUS ethambutol 15–25mg/kg body weight (max 2.5 gm/day) by mouth once daily **(AI)** followed by chronic suppressive therapy ***For Severe** Disease**, Add:*** • Rifabutin 10–20mg/kg body weight (max 300mg/day) by mouth once daily **(CI)**	• Azithromycin 10–12mg/kg body weight (max 500mg/day) by mouth once daily if intolerant to clarithromycin **(AII)** ***If rifabutin cannot be administered (or if a fourth drug is needed for patients with more severe symptoms or disseminated disease):*** • Ciprofloxacin 10–15mg/kg body weight by mouth twice daily (max 1.5 gm/day); or levofloxicin 500mg by mouth once daily; or amikacin 15–30mg/kg body weight IV in 1 or 2 divided doses (max 1.5 gm/day) **(CIII)**	• Combination therapy with a minimum of 2 drugs is recommended **(AI)** • Clofazamine is associated with increased mortality in HIV-infected adults and should not be used **(EII)** • Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination **(AIII)** • Fluoroquinolones (e.g., ciprofloxacin, levofloxacin) are not labeled for use in children <18 years due to concerns regarding potential effects on cartilage; use in younger persons requires an assessment of potential risks and benefits **(CIII)** • Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy (Table 2)

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
FUNGAL INFECTIONS			
Aspergillosis	• Voriconazole 6–8mg/kg body weight per dose IV or 8mg/kg body weight (max 400mg) per dose by mouth twice daily on day 1, followed by 7mg/kg body weight (max 200mg) per dose IV or orally twice daily **(AI)** ***Treatment** duration:* ≥12 weeks, but treatment duration should be individualized for each patient based on clinical response	• Amphotericin B deoxycholate 1–1.5mg/kg body weight IV once daily **(AIII)** • Lipid formulations of amphotericin B 5mg/kg body weight IV once daily **(AIII)** • Caspofungin 70mg/m^2 body surface area (max 70mg) IV as loading dose, then 50mg/m^2 body surface area (max 50mg) IV once daily	• Potential for significant pharmacokinetic interactions between protease inhibitors or non-nucleoside reverse transcriptase inhibitors with voriconazole, and it should be used cautiously in these situations. Consider therapeutic drug monitoring and dosage adjustment if necessary.
Candidiasis	*Oropharyngeal:* • Fluconazole 3–6mg/kg body weight (max 400mg/dose) by mouth once daily **(AI)** • Itraconazole cyclodextrin oral solution 2.5mg/kg body weight by mouth twice daily (max 200mg/day) **(AI)** • Clotrimazole trouches: 10mg troche by mouth 4 times daily **(BII)** • Nystatin suspension: 4–6 ml by mouth 4 times daily OR 1–2 200,000 U flavored pastilles by mouth 4–5 times daily **(BII)** ***Treatment** duration:* 7 to 14 days ***Esophageal** disease:* • Fluconazole 6mg/kg body weight by mouth once on day 1, then 3–6mg/kg body weight (max 400mg/dose) by mouth once daily **(AI)** • Itraconazole cyclodextrin oral solution 2.5mg/kg body weight by mouth twice daily or 5.0mg/kg body weight by mouth once daily **(AI)** ***Treatment** duration:* minimum of 4 to 21 days ***Invasive** disease:* • Amphotericin B 0.5–1.5mg/kg body weight IV once daily **(AI)** ***Treatment** duration:* Based on presence of deep tissue foci and clinical response; in patients with candidemia, treat until 2 to 3 weeks after last by positive blood culture **(AIII)**	*Oropharyngeal **(fluconazole-refractory):*** • Itraconazole cyclodextrin oral solution 2.5mg/kg body weight by mouth twice daily (max 200–400mg/day) **(AI)** • Amphotericin B oral suspension 1 ml (100mg/ml) by mouth 4 times daily **(BII)** ***Esophageal Disease:*** • Amphotericin B 0.3–0.5mg/kg body weight IV once daily **(BII)** ***Invasive Disease:*** • Fluconazole 5–6mg/kg body weight IV or by mouth twice daily (max 600mg/day) for minimum 4 weeks (if uncomplicated C. albicans candidemia) **(AI)** • Lipid formulations of amphotericin B 5mg/kg body weight IV once daily **(BII)** • Amphotericin B (as per preferred therapy dose) PLUS flucytosine 100–150mg/kg body weight by mouth divided into 4 doses for severe invasive disease, especially involving the central nervous system **(CIII)**	• Itraconazole cyclodextrin oral solution should not be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease **(DII)** • Central venous catheters should be removed when feasible in HIV-infected children with fungemia **(AII)** • Fluconazole should not be used for the empiric treatment of fungemia because resistance of non-albicans Candida species to fluconazole has been reported **(EIII)** • In uncomplicated catheter-associated *C. albicans* candidemia, an initial course of amphotericin B followed by fluconazole to complete treatment may be used **(BIII)** • Amphotericin B initiation doses: *Mild to moderate disease:* • Initiate at doses of 0.25–0.5mg/kg body weight IV once daily, then increase as tolerated to 0.5–1.5mg/kg body weight IV once daily **(BIII)** ***Severe disease:*** Initiate treatment at target daily dose **(BIII)** • Following stabilization and resolution of fever on daily therapy in children with invasive disease, amphotericin B may be given as 1.5 mg/kg body weight IV once every other day **(BIII)** • Lipid formulation of amphotericin B may be used in patients with renal insufficiency/infusion-related toxicity to amphotericin B **(BII)** • Voriconazole has been used for treatment of esophageal candidiasis in a small number of immunocompromised children without HIV infection; due to limited experience in children, data are insufficient to recommend use of this drug for esophageal or disseminated candidiasis **(CIII)** • Caspofungin has been used to treat esophageal and invasive candidiasis in adults but data in children are limited and definitive pediatric dose has not been defined **(CIII)** • Flucytosine dose should be adjusted to keep drug levels between 40–60μg/mL

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Coccidioides spp.	***Diffuse** Pulmonary **or Disseminated Non-Meningitic Disease:*** • Amphotericin B 0.5–1.0mg/kg body weight IV once daily until clinical improvement (minimum of several weeks) **(AII)** ***Meningeal** Infection:* • Fluconazole 5–6mg/kg body weight IV or by mouth twice daily (max 800mg/day) **(AII)**	*Diffuse Pulmonary or Disseminated Non-Meningitic Disease (in stable patient):* • Fluconazole 5–6mg/kg body weight IV or by mouth twice daily (max 800mg/day) **(BIII)** • Itraconazole 5–10mg/kg body weight IV or by mouth twice daily for 3 days, followed by 2–5mg/kg body weight by mouth twice daily (max 400mg/day) **(BIII)** ***Meningeal Infection (unresponsive to fluconazole):*** • Amphotericin B plus intrathecal amphotericin B **(CI)**	• Surgical debridement of bone and lung lesions may be helpful • Some experts add triazole to amphotericin B therapy, and continue triazole once amphotericin B is stopped **(BIII)** • May consider voriconazole, caspogungin, or posaconazole; or combinations, although experience in children is limited and definitive pediatric dose has not been defined **(CIII)** • Options should be discussed with an expert in the treatment of coccidioidomycosis • Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is recommended in adults and children following initial induction therapy (Table 2)
Cryptococcus neoformans	***Central Nervous** System **(CNS) Disease*** ***Acute Therapy (minimum 2 week induction followed by consolidation therapy):*** • Amphotericin B 0.7–1.0mg/kg body weight (or liposomal amphotericin B 6mg/kg body weight) IV daily PLUS flucytosine 100mg/kg body weight orally daily divided 4 times a day **(AI)** ***Consolidation** Therapy **(followed by chronic suppressive therapy):*** • Fluconazole 12mg/kg body weight on day 1 and then 6–12mg/kg body weight (max 800mg) daily IV or orally for a minimum of 8 weeks **(AI)** ***Localized disease including isolated pulmonary disease (CNS not involved)*:*** • Fluconazole 12mg/kg body weight on day 1 and then 6–12mg/kg body weight (max 600mg) IV or orally daily **(AIII)** ***Disseminated disease (CNS not involved) or severe, pulmonary disease*:*** • Amphotericin B 0.7–1.0mg/kg body weight or amphotericin liposomal 3–5mg/kg body weight or amphotericin lipid complex 5mg/kg body weight IV once daily (± flucytosine) **(AIII)** * Duration of ***initial*** therapy for non-CNS disease depends on site and severity of infection and clinical response	*Central **Nervous System (CNS) Disease*** ***Acute Therapy (minimum 2 week induction followed by consolidation therapy):*** • Liposomal amphotericin B 6mg/kg body weight IV once daily (especially in children with renal insufficiency or infusion-related toxicity to amphotericin B) **(AII)** • Amphotericin B 0.7–1.5mg/kg body weight IV once daily (if flucytosine not tolerated) **(BI)** • Fluconazole 12mg/kg body weight on day 1 and then 6–12mg/kg body weight (max 800mg) IV or orally daily PLUS flucytosine 100mg/kg body weight orally daily divided 4 times a day **(BII)** (offered only if amphotericin B-based therapy not tolerated) ***Consolidation Therapy (followed by chronic suppressive therapy):*** • Itraconazole 5–10mg/kg per day given once or twice daily (max 200mg/dose) for a minimum of 8 weeks **(BI)**. A loading dose (calculated twice daily dose is given 3 times daily) is given for the first 3 days (max 200mg/dose; 600mg/day). See comment on itraconazole under other options/issues. *Localized disease including isolated pulmonary disease (CNS not involved):* • Amphotericin B 0.7–1.0mg/kg body weight or amphotericin liposomal 3–5mg/kg body weight	• In patients with meningitis, CSF culture should be negative prior to initiating consolidation therapy • Overall *in vitro* resistance to antifungal agents used for treating of cryptococcosis remains uncommon. Newer azoles (voriconazole, posaconazole, ravuconazole) are all very active *in vitro* against *C. neoformans*, but there is limited published clinical experience regarding their use for cryptococcosis • Liquid preparation of itraconazole (if tolerated) preferable (but more expensive) over tablet formulation because of better bioavailability **(BIII)** • Serum concentrations of itraconazole should be monitored to optimize drug dosing • Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake or impairing its renal excretion or both • Flucytosine dose should be adjusted to keep drug levels at 40–60μg/mL • Oral acetazolamide should not be used for reduction of intracranial pressure in cryptococcal meningitis **(DIII)** • Chronic suppressive therapy (secondary prophylaxis) with fluconazole is recommended in adults and childrens following initial therapy (Table 2)

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Cryptococcus neoformans (con't)		or amphotericin lipid complex 5mg/kg body weight IV daily **(AIII)** ***Disseminated disease (CNS not involved) or severe, pulmonary disease:*** • Fluconazole 12mg/kg body weight on day 1 and then 6–12mg/kg body weight (max 600mg) IV or orally once daily **(AIII)**	
Histoplasma capsulatum	***Mild** Disseminated **Disease*** • Intraconazole oral solution: initial loading dose of 2–5mg/kg body weight per dose (max 200mg) by mouth 3 times daily for first 3 days of therapy, followed by 2–5mg/kg body weight (max 200mg) per dose given twice daily for 12 months **(AII)** ***Moderately Severe to Severe Disseminated Disease*** ***Acute Therapy (**minimum **1 to 2 week induction, longer if clinical improvement is delayed, followed by consolidation therapy):*** • Lipsomal amphotericin B 3mg/kg body weight IV once daily **(AI)** ***Consolidation** Therapy **(followed by chronic suppressive therapy):*** • Intraconazole oral solution: initial loading dose of 2–5mg/kg body weight per dose (max 200mg) by mouth 3 times daily for first 3 days of therapy, followed by 2–5mg/kg body weight (max 200mg) per dose given twice daily for 12 months **(AII)** ***Central Nervous** System **Infection*** ***Acute Therapy (4** to **6 weeks, followed by consolidation therapy):*** • Lipsomal amphotericin B 5mg/kg body weight IV once daily **(AII)** ***Consolidation** Therapy **(followed by chronic suppressive therapy):*** • Intraconazole oral solution: initial loading dose of 2–5mg/kg body weight per dose (max 200mg) by mouth 3 times daily for first 3 days of therapy, followed by 2–5mg/kg body weight (max 200mg) per dose given twice daily for ≥12 months and histoplasmal antigen is no longer detected **(AII)**	*Mild **Disseminated Disease*** • Fluconazole 5–6mg/kg body weight IV or by mouth per dose given twice daily (max 800mg/day) for ≥12 months **(CII)** ***Moderately Severe to Severe Disseminated Disease or CNS Infection*** ***Acute Therapy (minimum 1 to 2 week induction, longer if clinical improvement is delayed or at least 4 to 6 weeks if CNS involvement, followed by consolidation therapy):*** • Amphotericin B deoxycholate 1.0mg/kg body weight IV once daily **(AIII)**	• Urine antigen should be monitored to identify relapse • Serum concentrations of itraconazole should be monitored and achieve a level of 1.0µg/mL at steady- state. Levels exceeding 10.0µg/mL should be followed by dose reduction. • Urine antigen should be monitored to identify relapse • High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered • Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy (Table 2)

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Pneumocystis pneumonia	• Trimethoprim-sulfamethoxazole (TMP-SMX) 15–20mg/kg body weight TMP PLUS 75–100mg/kg body weight SMX daily given IV or by mouth in 3–4 divided doses **(AI)** (after acute pneumonitis resolved in mild-moderate disease, IV TMP-SMX may be changed to oral) ***Treatment duration (followed by chronic suppressive therapy):*** 21 days **(AII)**	***Alternative Therapeutic Regimens (if TMP-SMX intolerant or clinical treatment failure after 5 to 7 days of TMP-SMX therapy):*** • Pentamidine 4mg/kg body weight IV once daily is first choice alternative regimen **(AI)** (pentamidine may be changed to atovaquone after 7 to 10 days IV therapy **[BIII]**) • Atovaquone 30–40mg/kg body weight (max 1,500mg/day) daily by mouth in 2 divided doses with food for patients from birth to 3 months and ≥24 months of age **(BI)**. For infants from 3 to 24 months, an increased dose of 45mg/kg body weight daily in 2 divided doses with food is needed **(AII)**	• Dapsone 2mg/kg body weight by mouth once daily (max 100mg/day) PLUS trimethoprim 15mg/kg body weight by mouth per day divided into 3 doses has been used in adults **(BI)**, but data in children are limited **(CIII)** • Primaquine base 0.3mg/kg body weight by mouth once daily (max 30mg/day) PLUS clindamycin 10mg/kg body weight IV or by mouth (max 600mg given IV and 300–450mg given orally) every 6 hours has been used in adults **(BI)**, but data in children are not available **(CIII)** • Indications for corticosteroids **(AI)**: o PaO2 <70 mmHg at room air or alveolar-arterial oxygen gradient >35 mmHg o *Prednisone dose:* 1mg/kg body weight by mouth twice daily for 5 days, then 0.5–1mg/kg body weight by mouth twice daily for 5 days, then 0.5mg/kg body weight by mouth once daily for days 11 to 21 • Chronic suppressive therapy (secondary prophylaxis) with TMP/SMX is recommended in children and adults following initial therapy (Table 2) **(AI)**
PARASITIC INFECTIONS			
Cryptosporidiosis	• Effective HAART therapy: Immune reconstitution may lead to microbiologic and clinical response **(AII)**	There is no consistently effective therapy for cryptosporidiosis in HIV-infected individuals; optimized HAART and a trial of nitazoxanide can be considered: • Nitazoxanide (data from immunocompetent children) (**BI**, HIV-uninfected; **CIII**, HIV-infected) in combination with effective HAART therapy: 1–3 yr: 100 mg by mouth twice daily 4–11 yr: 200 mg by mouth twice daily >12 yr: 500 mg by mouth twice daily *Treatment duration:* ***trial of ≤14 days***	• Supportive care: Hydration, correct electrolyte abnormalities, nutritional support **(AIII)** • Antimotility agents (e.g., loperamide) should be used with caution among young children **(CIII)**
Malaria	*Uncomplicated* ***P. falciparum OR unknown malaria species, from Chloroquine resistant (all other malaria areas, or unknown region):*** • Atovaquone-proguanil (Malarone™) (pediatric tablets 62.5mg/25mg; adult tablets 250mg/100mg adult tabs): 5– 8 kg, 2 peds tabs x 3 days; 9–10 kg, 3 peds tabs x 3 days; 11–20 kg, 4 peds tabs or 1 adult tab x 3 days; 21–30	*Uncomplicated* ***P. falciparum OR unknown malaria species, chloroquine resistant (all other malaria areas, or unknown region)*** • Mefloquine (Larium™) (250mg tablets only): 15mg/kg body weight (max 750mg) by mouth once, then 10mg/kg body weight (max 500mg) by mouth given 12 hrs later • Quinine sulfate 10mg/kg body weight (max	• Chloroquine phosphate is the only formulation of chloroquine available in the United States. 10mg of chloroquine phosphate = 6mg of chloroquine base • Doxcycline should be used in persons >8 years of age. The alternative is clindamycin 20mg/kg divided Q 8 hrs. • Papua New Guinea has widespread chloroquine resistant *P. vivax*, thus should be treated as chloroquine resistant malaria • Before primaquine is given, G6PD status must be verified. Primaquine is typically given following the initial chloroquine

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Malaria (con't)	kg, 2 adult tabs x 3 days; 31–40 kg, 3 adult tabs x 3 days; >40 kg, 4 adult tabs x 3 days ***Chloroquine sensitive region (North of the Panama Canal):*** • Chloroquine phosphate 16.6mg/kg (10mg/kg body weight base) (max 1,000mg) by mouth once, then 8.3mg/kg body weight (max 500mg) by mouth at 6, 24, 48 hours (total dose = 41.6mg/kg chloroquine phosphate [max 2,500mg] = 25mg/kg chloroquine base) ***P. vivax, P. ovale, P. malariae (all areas except Papua New Guinea, Indonesia)*** ***Initial therapy (followed by anti-relapse therapy):*** • Chloroquine phosphate 16.6mg (10mg/kg body weight base) (max 1,000mg) by mouth once, then 8.3mg/kg body weight (max 500mg) by mouth at 6, 24, 48 hours (total dose = 41.6mg/kg body weight chloroquine phosphate [max 2,500mg] = 25mg/kg body weight chloroquine base) *Anti-relapse therapy for P. ovale, P. vivax* • Primaquine 0.5mg base/kg body weight (max 30mg base) by mouth daily for 14 days	650mg) by mouth every 8 hrs for 3 to 7 days PLUS clindamycin 20mg/kg body weight daily by mouth divided into 3 doses given every 8 hrs for 7 days	blood phase therapy, not in combination. • For most updated prevention and treatment recommendations for specific region, refer to updated CDC treatment table available from: http://www.cdc.gov/malaria/pdf/treatmenttable.pdf
	Severe malaria • Quinidine gluconate 10mg/kg body weight IV loading dose over 1 to 2 hrs, then 0.02mg/kg/minute infusion for ≥24 hours (***Treatment duration:*** 7 days in Southeast Asia, Oceania, otherwise 3 days) PLUS doxycycline 100mg per dose by mouth every 12 hours for 7 days or clindamycin 20mg/kg body weight daily by mouth divided into 3 doses given every 8 hrs for 7 days. Quinidine gluconate 10mg = 6.25mg quinidine base.	***Severe malaria*** • Quinidine 6.25mg base/kg body weight IV loading dose over 1 to 2 hrs, then 0.0125mg/kg /minute infusion (***Treatment duration:*** 7 days in Southeast Asia, Oceania, otherwise 3 days) PLUS doxycycline 100mg per dose by mouth every 12 hours for 7 days or clindamycin 20mg/kg body weight daily by mouth divided into 3 doses given every 8 hrs for 7 days • Artesunate 2.4mg/kg body weight IV bolus at 0, 12, and 24 hrs then once daily for 7 days; when able to take an oral regimen, may switch to either artesunate 2mg/kg body weight by mouth once daily PLUS doxycycline 100mg per dose by mouth every 12 hrs OR Mefloquine 15mg/kg body weight (max 750mg) by mouth once, then 10mg/kg body weight (max 500mg) by mouth once given 12 hrs later	• Quinidine gluconate is a class 1a anti-arrhythmic agent not typically stocked in pediatric hospitals. When regional supplies are not available, this can be obtained from Eli Lilly Company, telephone: 800-821-0538 and the CDC Malaria hotline may be of assistance (see below). Do not give quinidine gluconate as an IV bolus. Quinidine gluconate IV should be administered in a monitored setting. Cardiac monitoring required. Adverse events include: severe hypoglycemia, prolongation of the QT interval, ventricular arrhythmia, and hypotension, and can result from the use of this drug at treatment doses. • Artesunate is available from CDC Quarantine stations, only as of July 2007. Contact the CDC Malaria Hotline 770-488-7788 from 8 am–4:30 pm EST or 770-488-7100 after hours, weekends, and holidays.

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Microsporidiosis	• Effective HAART therapy: Immune reconstitution may lead to microbiologic and clinical response **(AII)** ***For disseminated (not ocular) and intestinal infection attributed to microsporidia other than Enterocytozoon bienuesi*** • Albendzaole 7.5mg/kg body weight (max 400 mg/dose) per dose by mouth twice daily **(AII)** ***Treatment duration:*** Continue until immune reconstitution after initiation of HAART **(AIII)** ***For ocular infection:*** • Topical fumagillin bicylohexylammonium (Fumidil B) 3mg/mL in saline (fumagillin 70μg/ml) eye drops – 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **(BII)** + Albendazole 7.5mg/kg body weight (max 400mg/dose) by mouth twice daily for management of systemic infection **(BIII)** ***Treatment duration:*** Continue indefinitely to prevent recurrence or relapse **(BIII)**		• Supportive care: Hydration, correct electrolyte abnormalities, nutritional support **(AIII)** • Antimotility agents (e.g., loperamide) should be used with caution among young children **(CIII)** • Fumagillin (adult dose, 20mg by mouth 3 times daily), or TNP-470 (a synthetic analogue of fumagillin) recommended for treatment of infections due to *Enterocytozoon bienuesi* in HIV-infected adults, is unavailable in the United States, and data on dosing in children is unavailable **(CIII)**
Toxoplasma gondii	***Congenital Toxoplasmosis* (AII)** • Pyrimethamine loading dose: 2mg/kg body weight by mouth once daily for 2 days, then 1mg/kg body weight by mouth once daily for 2–6 months, then 1mg/kg body weight by mouth 3 times weekly PLUS leucovorin (folinic acid) 10mg by mouth or IM with each dose of pyrimethamine PLUS sulfadiazine 50mg/kg body weight by mouth twice daily ***Treatment duration:*** 12 months **(AII)** ***Acquired Toxoplasmosis*** ***Acute Induction Therapy (followed by chronic suppressive therapy)* (AI):** • Pyrimethamine: loading dose, 2mg/kg body weight (max 50mg) by mouth once daily for 3 days, then 1mg/kg body weight (max 25mg) by mouth once daily PLUS sulfadiazine 25–50mg/kg body weight (max 1–1.5 gm/dose) by mouth per dose 4 times daily PLUS leucovorin	***For Sulfonamide-Intolerant Patients*** • Clindamycin 5–7.5mg/kg body weight (max 600mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leukovorin **(AI)**	***Congenital Toxoplasmosis*** • For infants born to mother with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mothers treatment during pregnancy **(BIII)** ***Acquired Toxoplasmosis*** • Pyrimethamine use requires complete blood count monitoring at least weekly on daily dosing and at least monthly while on less than daily dosing **(AIII)** • TMP-SMX (5mg/kg body weight TMP plus 25mg/kg body weight SMX per dose IV or by mouth given twice daily) has been used as an alternative to pyrimethamine-sulfadiazine in adults **(BI)**, but has not been studied in children **(CIII)** • Atovaquone (adults, 1.5 gm by mouth twice daily) in regimens combined with pyrimethamine/leukovorin; with sulfadiazine alone; or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, have been used in adults **(BII)**, but these regimens have not been studied in children **(CIII)** • Azithromycin (adults, 900–1,200mg/day) has also been used in

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Toxoplasma gondii (con't)	10–25mg by mouth daily, followed by chronic suppressive therapy ***Treatment** duration **(followed by chronic suppressive therapy):*** ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks) **(BII)**		adults combined with pyrimethamine-sulfadiazine **(BII)**, but has not been studied in children **(CIII)** • Corticosteriods (e.g., prednisone or dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible **(BIII)** • Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continue through the acute treatment; but should not be used prophylactically **(DIII)** • Chronic suppressive therapy (secondary prophylaxis) is recommended in adults and children following initial therapy **(AI)**
VIRAL INFECTIONS			
Cytomegalovirus (CMV)	*Symptomatic **Congenital Infection with Neurologic Involvement*** • Ganciclovir 6mg/kg body weight IV every 12 hours for 6 weeks **(BI)** ***Disseminated Disease and Retinitis*** ***Induction Therapy (followed by chronic suppressive therapy):*** • Ganciclovir 5mg/kg body weight IV every 12 hours for 14 to 21 days (may be increased to 7.5mg/kg body weight IV twice daily), then 5mg/kg per day for 5 to 7 days per week for chronic suppression **(AI)** ***Central Nervous** System **Disease (followed by chronic suppressive therapy)*** • Ganciclovir 5mg/kg body weight IV every 12 hours PLUS foscarnet 60mg/kg body weight IV every 8 hours, continued until symptomatic improvement **(BII)**, followed by chronic suppression	*Disseminated **Disease and Retinitis*** ***Induction Therapy (followed by chronic suppressive therapy):*** • Foscarnet 60mg/kg body weight IV every 8 hours for 14 to 21 days**,** then 90–120mg/kg once a day for chronic suppression **(AI)** ***Alternative for Retinitis (followed by chronic suppressive therapy):*** • IV ganciclovir plus IV foscarnet (at above induction doses) may be considered as initial induction therapy in children with sight-threatening disease **(BIII)** • Older children: Gancilovir intraocular implant PLUS oral ganciclovir 30mg/kg 3 times daily **(BIII)** or if old enough to receive adult dosing, oral valganciclovir 900mg by mouth once daily **(AI)**	• Valganciclovir is used in adults for treatment of CMV retinitis: induction dosing in adults is 900mg by mouth twice daily for 14 to 21 days, followed by chronic suppressive therapy **(AI)**; however, data on valganciclovir dosing in children is unavailable **(CIII)**. Valganciclovir liquid formulation not commercially available, and since pharmacokinetics, bioavailability, safety, and shelf-life of extemporaneously compounded valganciclovir not known, such "homebrew" formulations should not be used **(EIII)**. • Cidofovir is also used for treatment of CMV retinitis in adults: induction dosing in adults is 5mg/kg body weight IV once weekly for 2 weeks, followed by chronic suppressive therapy **(AI)**; however, data on dosing in children is unavailable **(CIII)**. Must be given with probenecid and IV hydration. • Intravitreal injections not practical for most children **(DIII)** • Intraocular implant should not be used in children <3 years of age due to small size of eyes **(EIII)** • Combination ganciclovir and foscarnet is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children is unknown, particularly if receiving optimized antiretroviral therapy • Chronic suppressive therapy (secondary prophylaxis) is recommended in adults and children following initial therapy of disseminated disease or retinitis (Table 2) **(AI)**

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Hepatitis B Virus (HBV)	***Treatment of HBV only required (does not require HAART)*** • Interferon-alfa: 3 million units/m^2 body surface area subcutaneously 3 times a week for 1 week, followed by dose escalation to 6 million units/m^2 (max 10 million units/dose), to complete a 24-week course **(BII)**; or • Adefovir 10mg by mouth once daily for older children who can receive adult dosing for a minimum of 12 months **(BII)**; ***Treatment of both HIV and HBV required*** • Lamivudine (3TC) 4mg/kg body weight by mouth (max 150mg/dose) twice daily as part of a fully suppressive HAART regimen **(BII)** • Include tenofovir 300mg by mouth once daily as part of HAART regimen with 3TC for older children who can receive adult dosing **(BII)** • If child is on HAART containing 3TC or emtricitabine (FTC) and has detectable HBV DNA (assume 3TC/FTC resistance): • If child old enough to receive adult dosing: continue 3TC (or FTC) **(CIII)** and if not on tenofovir, add tenofovir 300mg by mouth once daily as part of HAART regimen **(BII)**; or add adefovir 10mg by mouth once daily in addition to HAART regimen **(BII)** • If child not old enough to receive adult dosing: give 6 month course of interferon-alfa as above in addition to HAART regimen **(BII)** *Treatment of HIV **alone*** • HAART regimen that avoids the use of 3TC, FTC, or tenofovir PLUS 6 month course of interferon-alfa as above; or adefovir 10mg by mouth once daily for older children who can receive adult dosing **(CIII)** • Alternatively, treat as above for HIV and HBV **(CIII)**, particularly if 2 anti-HBV drugs can be given **(BII)**	• Interferon-alfa 10 million units/m^2 body surface area subcutaneously 3 times a week for 6 months (sometime used for re-treatment of failed lower dose interferon therapy) **(CII)** • Alternative for 3TC: FTC 6mg/kg body weight (max 200mg) once daily **(BII)**	• Indications for treatment include **(BII)**: o Detectable serum HBV DNA, with or without + HBeAg, for >6 months; and o Persistent (>6 months) elevation of serum transaminases (≥twice the upper limit of normal); or o Evidence of chronic hepatitis on liver biopsy • Interferon-alfa is contraindicated in children with decompensated liver disease, significant cytopenias, severe renal, neuropsychiatric, or cardiac disorders, and autoimmune disease **(EII)** • Choice of HBV treatment options for HIV/HBV-coinfected children depends upon whether concurrent HIV treatment is warranted • 3TC and FTC have similar activity (and have cross-resistance) and should not be given together • Tenofovir is not approved for use in HIV-infected children <18 years and there is no pediatric formulation; it can be used for older HIV-infected children who can receive adult dosage • Adefovir is not approved for use in children, but is under study in HIV-uninfected children for treatment of chronic hepatitis B; can be considered for older HIV-infected children who can receive adult dosage • Immune reconstitution inflammatory syndrome (IRIS) may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6 to 12 weeks of HAART. It may be difficult to distinguish between drug-induced hepatotoxicity or other causes of hepatitis and IRIS • In children receiving 3TC, FTC, and/or tenofovir, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HIV/HBV 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 anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening **(BIII)** • Entecavir and telbivudine have been approved for use in adults with HBV; there are no data on safety or efficacy of these medications in children

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Hepatitis C Virus (HCV)	*Interferon-alfa plus ribavirin combination therapy* **(AII)** • Interferon-alfa–2a or –2b, 3–5 million units/m^2 body surface area subcutaneously or IM 3 times a week (max 3 million units/dose) PLUS • Ribavirin (oral) 15mg/kg body weight weight daily given in 2 divided doses (fixed dose by weight recommended): 25–36 kg: 200 mg AM and PM >36–49 kg: 200 mg in AM and 400 mg in PM >49–61 kg: 400 mg in AM and PM >61–75 kg: 400 mg in AM and 600 mg in PM >75 kg: 600 mg in AM and PM ***Treatment** duration**:*** 48 weeks, regardless of HCV genotype **(BIII)**	*For children in whom ribavirin is contraindicated (e.g., unstable cardiopulmonary disease, pre-existing anemia or hemoglobinopathy)* • Interferon-alfa–2a or –2b 3–5 million units/m^2 body surface area (max 3 million units/dose) subcutaneously or IM 3 times a week **(BII)**	• Length of treatment for HIV/HCV-coinfected children is unknown and based on recommendations for HIV/HCV-coinfected adults **(BIII)** • Treatment of HCV in children <3 years is generally not recommended **(DIII)** • Indications for treatment are based on recommendations in HIV/HCV-coinfected adults; since HCV therapy is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-infected children >3 years in whom there are no contraindications to treatment **(AIII)** • IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6 to 12 weeks of HAART. It may be difficult to distinguish between drug-induced hepatotoxicity or other causes of hepatitis and IRIS. • Interferon-alfa is contraindicated in children with decompensated liver disease, significant cytopenias, severe renal or cardiac disorders and autoimmune disease **(EII)** • Ribavirin is contraindicated in children with unstable cardiopulmonary disease, severe pre-existing anemia or hemoglobinopathy **(EII)** • Didanosine combined with ribavirin may lead to increased mitochondrial toxicities; concomitant use is contraindicated **(EI)** • Ribavirin and zidovudine both are associated with anemia and when possible should not be administered together **(BII)** • Pegylated interferon-alfa is not currently approved for use in children although it is under study; in adults, pegylated interferon-alfa–2a (180mcg) or –2b (1.5mcg/kg) given subcutaneously once weekly plus ribavirin is the treatment of choice in adults with chronic HCV hepatitis warranting treatment **(AI)**

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Herpes Simplex Virus (HSV)	***Neonatal Central** Nervous **System or Disseminated Disease*** • Acyclovir 20mg/kg body weight IV per dose 3 times daily for 21 days **(AI)** ***Neonatal Skin, Eye, or Mouth Disease*** • Acyclovir 20mg/kg body weight IV per dose 3 times daily for 14 days **(AI)** ***Central Nervous** System **or Disseminated Disease in Children Outside the Neonatal Period*** • Acyclovir 10mg/kg body weight IV 3 times daily for 21 days **(AII)** ***Moderate to Severe** Symptomatic **Gingivostomatitis*** • Acyclovir 5–10mg/kg body weight per dose IV 3 times daily **(AI)** • After lesions began to regress, change to oral acyclovir **(AI)**; continue therapy until lesions have completely healed ***For Genital Herpes (**Adults **and Adolescents)*** • Acyclovir 20mg/kg body weight (max 400mg/dose) per dose by mouth 3 times daily for 5 to 14 days **(AI)**	***Acyclovir-Resistant HSV Infection*** • Foscarnet 40mg/kg body weight per dose given IV 3 times daily or 60mg/kg body weight per dose given IV twice daily **(AI)** ***Mild Symptomatic Gingivostomatitis*** • Acyclovir 20mg/kg body weight (max 400mg/dose) per dose by mouth 3 times daily for 5 to 10 days **(AI)**	• For neonatal central nervous system disease: Repeat CSF HSV DNA PCR should be performed at days 19 to 21 of therapy; do not stop acyclovir until repeat CSF HSV DNA PCR is negative **(BIII)** • Valacyclovir is approved for use in adult and adolescents with mucocutaneous HSV at a dose of 1 gram by mouth twice daily **(AI)**; there is no pediatric preparation and data on dosing in children is limited; could be used by older children able to receive adult dosing • Famciclovir is approved for use in adults and adolescents with mucocutaneous HSV infection at a dose of 500mg by mouth twice daily **(AI)**; there is no pediatric preparation and data on dosing in children is unavailable; could be used by older children able to receive adult dosing • Suppressive secondary prophylaxis can be considered for children with severe and recurrent gingivostomatitis **(AI)**
Human Papillomavirus (HPV)	• Podofilox solution/gel (0.5%) applied topically twice daily for 3 consecutive days a week for ≤4 weeks (patient applied) **(BIII)** • Imiquimod cream (5%) applied topically at night and washed off in the morning for 3 non-consecutive nights a week for up to 16 weeks (patient applied) **(BII)** • Trichloroacetic acid applied topically weekly for up to 3 to 6 weeks **(BIII)** • Podophyllin resin 10%–25% suspension in tincture of benzoin applied topically and washed off several hours later repeated weekly for 3 to 6 weeks **(CIII)**	• Individual external genital wart lesions can be removed by cryotherapy or electrodessication; may be repeated every 1 to 2 weeks **(BIII)** • Veragen self-applied 3 times daily for up to 16 weeks (patient applied) **(CIII)** • Laser ablation or surgical excision for recalcitrant cases	• Adequate topical anesthetics to the genital area should be given prior to the application of caustic modalities • Intra-lesional interferon-alpha: Generally not recommended because of high cost, difficult administration, and potential for systemic side effects **(DIII)** • Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults, but is not commercially available and has very limited use in children; systemic absorption can occur **(CIII)** • HAART has not been consistently associated with reduced risk of HPV-related cervical abnormalities in HIV-infected women • Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removal of all disease. Adjuvant therapy with interferon-alfa or intralesional cidofovir is being used investigationally for invasive disease **(CIII)**. • Abnormal Pap smear cytology should be referred to colposcopy for diagnosis and management

Pathogen	Preferred Therapies and Duration	Alternative Therapies	Other Options/Issues
Varicella Zoster Virus (VZV)	***Chickenpox*** ***Children with No or Moderate** Immune **Suppression (CDC Immunologic Categories 1 and 2** [985]**) and Mild Varicella Disease (oral** **[BIII])*:** • Acyclovir 20mg/kg body weight by mouth per dose (max 800mg/dose) 4 times daily for 7 to 10 days or until no new lesions for 48 hours **(AI)** ***Children with Severe Immune Suppression (CDC Immunologic Category 3** [985]**, IV** **[AIII])*:** • Acyclovir 10mg/kg body weight IV per dose 3 times daily for 7 to 10 days or until no new lesions for 48 hours **(AI)** ***Zoster*** ***Children with Trigeminal Nerve Involvement or Extensive Multi-Dermatomal Zoster (IV** **[AII])*:** • Acyclovir 10mg/kg body weight IV per dose 3 times daily until cutaneous lesions and visceral disease are clearly resolving, when can switch to oral acyclovir to complete 10 to 14 day course **(AII)** ***Children with Progressive Outer** Retinal **Necrosis (PORN):*** • Ganciclovir 5mg/kg body weight IV every 12 hours, PLUS foscarnet 90mg/kg body weight IV every 12 hours, PLUS ganciclovir 2mg/0.05mL intravitreal twice weekly, and/or foscarnet 1.2mg/0.05mL intravitreal twice weekly **(AIII)** ***Children with Acute Retinal N**ecrosis **(ARN):*** • Acyclovir 10mg/kg body weight IV 3 times daily for 10 to 14 days, followed by oral valacyclovir 1 gm per dose 3 times daily for 4 to 6 weeks (for children old enough to receive adult dose; alternative oral acyclovir 20mg/kg body weight for 4 to 6 weeks **(AIII)**	***For Patients Not Responding to Acyclovir*** • Foscarnet 40–60mg/kg body weight IV per dose 3 times daily for 7 to 10 days **(AI)**	• Some experts base IV acyclovir dosing in children ≥1 year on body surface area (500mg/m^2/dose IV every 8 hours) instead of body weight • Valacyclovir is approved for use in adult and adolescents with zoster at a dose of 1 gm by mouth twice daily for 7 to 10 days **(AII)**; there is no pediatric preparation and data on dosing in children is limited; could be used by older children able to receive adult dosing • Famciclovir is approved for use in adults and adolescents with zoster at a dose of 500mg by mouth 3 times daily for 7 to 10 days **(AII)**; there is no pediatric preparation and data on dosing in children is limited; could be used by older children able to receive adult dosing • Involvement of an experienced ophthalmologist with management of children with VZV retinitis is strongly recommended **(AIII)**

***** Note: Information contained in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for products or indications. Specifically the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval. Letters and Roman numerals in parentheses after regimens indicate the strength of the recommendations and the quality of evidence supporting it (see Box in Introduction).

gm: Gram; HAART: Highly active antiretroviral therapy; kg: Kilogram; mg: Milligram; PCR: Polymerase chain reaction

TABLE 5. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Anti-Fungal Drugs				
Amphotericin B Deoxycholate (Fungizone)	*Intravenous*	*Frequent:* • Infusion-related reactions (fever/chills; nausea/vomiting; hypotension; anaphylaxis) • Anemia • Hypokalemia • Renal function impairment • Thrombophlebitis (at injection site) *Less frequent/rare:* • Blurred or double vision • Cardiac arrhythmias, usually with rapid infusions • Hypersensitivity (rash) • Leukopenia • Polyneuropathy • Seizures • Thrombocytopenia	• Gastrointestinal disturbance (nausea, vomiting, diarrhea, abdominal pain) • Headache	• Infuse over 1 to 2 hours; in patients with azotemia, hyperkalemia, or getting doses >1mg/kg, infuse over 3 to 6 hours • Requires dose reduction in patients with impaired renal function • Nephrotoxicity exacerbated with concomitant use of other nephrotoxic drugs, avoid when possible; permanent nephrotoxicity related to cumulative dose • Nephrotoxicity may be ameliorated by hydration with 0.9% saline intravenously over 30 minutes prior to the amphotericin B infusion • Infusion-related reactions less frequent in children than adults; onset usually 1 to 3 hours after infusion, duration <1 hour; frequency decreases over time • Pretreatment with acetaminophen and/or diphenhydramine may alleviate febrile reactions
Amphotericin B lipid complex (Abelcet)	*Intravenous*	*More frequent:* • Infusion-related reactions (fever/chills, nausea/vomiting; headache, nausea and vomiting) *Less frequent:* • Anemia • Leukopenia • Respiratory distress • Thrombocytopenia • Renal function impairment	• Gastrointestinal disturbance (loss of appetite, nausea, vomiting, diarrhea, abdominal pain)	• Infuse diluted solution at rate of 2.5mg/kg/hour • In-line filters should not be used • Use with caution with other drugs that are bone marrow suppressants or that are nephrotoxic; renal toxicity dose-dependent, but less renal toxicity than seen with conventional amphotericin B • Consider dose reduction in patients with impaired renal function

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Amphotericin B liposome (AmBisome)	*Intravenous*	*More frequent:* • Fever, chills • Hypokalemia *Less frequent:* • Back pain • Chest pain • Dark urine • Dyspnea • Infusion-related reaction (fever/chills, headache) • Jaundice • Renal function impairment *Rare:* • Anaphylactic reaction	• Gastrointestinal disturbance (nausea, vomiting, diarrhea, abdominal pain) • Headache • Skin rash	• Infuse over 2 hours • Consider dose reduction in patients with impaired renal function
Caspofungin (Cancidas)	*Intravenous*	*More frequent:* • Histamine-mediated symptoms (fever, facial swelling, pruritis, bronchospasm) *Rare:* • Hypokalemia • Anaphylactic reaction	• Gastrointestinal disturbances (nausea, vomiting, diarrhea) • Headache • Skin rash, facial flushing • Elevated liver transaminases • Thrombophelbitis	• Requires dose adjustment in moderate-to-severe hepatic insufficiency • Intravenous infusion over 1 hour in normal saline (do not use diluents containing dextrose)
Flucytosine (Ancobon)	*Capsules:* 250mg, 500mg	*More frequent:* • Bone marrow suppression (especially leukopenia and thrombocytopenia) *Less frequent:* • Hepatotoxicity • Renal toxicity (including crystalluria) *Rare:* • Cardiac toxicity (ventricular dysfunction, myocardial toxicity, cardiac arrest) • Central nervous system symptoms (hallucinations, seizures, peripheral neuropathy) • Anaphylaxis	• Gastrointestinal disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) • Elevated liver transaminases • Skin rash *Rare:* • Central nervous system symptoms (headache, drowsiness, confusion, vertigo)	• Drug levels should be monitored and doses adjusted to maintain at 40–60μg/mL • Requires dose adjustment in patients with impaired renal function; use with extreme caution • Fatal aplastic anemia and agranulocytosis have been rarely reported

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Fluconazole (Diflucan)	*Oral suspension:* 10mg/mL, 40mg/mL *Tablets:* 50mg, 100mg, 150mg, 200mg *Intravenous*	*Infrequent:* • Hypersensitivity (fever, chills, skin rash) *Rare:* • Agranulocytosis • Exfoliative skin disorders (including Stevens-Johnson Syndrome) • Hepatotoxicity • Thrombocytopenia	*Frequent:* • Gastrointestinal disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) *Infrequent:* • Central nervous system effects (dizziness, drowsiness, headache) • Alopecia	• May be given orally without regard to meals • Requires dose adjustment in patients with impaired renal function • Intravenous administration should be administered once daily at rate ≤200 mg/hour • Oral and intravenous doses are the same • Multiple potential drug interactions
Itraconazole (Sporanox)	*Oral solution:* 10mg/mL *Capsules:* 100mg *Intravenous*	*Infrequent:* • Hypersensitivity (fever, chills, skin rash) • Hypokalemia (can be associated with cardiac arrhythmias) *Rare:* • Hepatotoxicity • Hematologic abnormalities (thrombocytopenia, leukopenia)	*Frequent:* • Gastrointestinal disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) *Infrequent:* • Central nervous system effects (dizziness, drowsiness, headache)	• Oral solution: give on an empty stomach as gastric acid increases absorption • Capsules: administer after a full meal to increase absorption • Itraconazole oral solution has 60% greater bioavailability compared with capsules, and the oral solution and capsules should not be used interchangeably • Intravenous infusion over 60 minutes • Multiple potential drug interactions
Posaconazole (Noxafil)	*Oral solution:* 40mg/mL	*Infrequent:* • Hypersensitivity (fever, chills, skin rash) • Anaphylactoid reaction with intravenous infusion *Rare:* • Hepatotoxicity (including hepatic failure) • Exfoliative skin disorders (including Stevens-Johnson Syndrome) • Renal dysfunction • Cardiac arrhythmias (QT prolongation, torsades de pointes) • Hemolytic uremic syndrome • Pulmonary embolism	• Bone marrow suppression • Muscular pain	• Must be given with meals. Adequate absorption is dependent on food for efficacy. • Liver function tests, renal function tests and electrolytes should be monitored while on therapy

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Ketoconazole (Nizoral)	*Tablets:* 200mg	*Infrequent:* • Hypersensitivity (fever, chills, skin rash) *Rare:* • Hepatotoxicity (including hepatic failure)	*Frequent:* • Gastrointestinal disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) *Infrequent:* • Central nervous system effects (dizziness, drowsiness, headache) *Rare:* • Gynecomastia • Impotence • Menstrual irregularities • Photophobia	• Adverse GI effects occur less often when administered with food • Drugs that decrease gastric acidity or sucralfate should be administered ≥2 hours after ketoconazole • Disulfiram reactions have occurred in patients ingesting alcohol • Hepatotoxicity is an idiosyncratic reaction, usually reversible when stopping the drug, but rare fatalities can occur any time during therapy; more common in females and adults >40 years, but cases reported in children • High dose ketoconazole suppresses corticosteroid secretion, lowers serum testosterone concentration (reversible) • Multiple potential drug interactions
Voriconazole (VFEND)	*Tablet:* 50mg, 200mg *Intravenous*	*Infrequent:* • Hypersensitivity (fever, chills, skin rash) • Anaphylactoid reaction with intravenous infusion *Rare:* • Hepatotoxicity (including hepatic failure) • Exfoliative skin disorders (including Stevens-Johnson Syndrome) • Renal dysfunction • Cardiac arrhythmias	*More frequent:* • Visual changes, dose-related (photophobia, blurry vision) • Central nervous system effects (dizziness, drowsiness, headache) • Gastrointestinal disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) *Rare:* • Gynecomastia	• Approved for use in treatment of aspergillosis and serious fungal infections caused by *Fusarium* species and *Scedosporium apiospermum* in adults intolerant or refractory to other therapy • Oral tablets should be taken 1 hour before or after a meal • Maximum infusion rate 3mg/kg/hour over 1 to 2 hours • Oral administration to patients with impaired renal function if possible (accumulation of intravenous vehicle occurs in patients with renal insufficiency) • Dose adjustment needed if hepatic insufficiency • Data in children not yet available • Visual disturbances common (>30%) but transient and reversible when drug is discontinued • Multiple potential drug interactions

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Anti-Pneumocystis Drugs				
Atovaquone (Mepron)	*Oral suspension:* 150mg/mL	*Frequent:* • Fever • Skin rash	*Frequent:* • Gastrointestinal disturbances (nausea, vomiting, diarrhea) • Headache • Cough • Insomnia	• Should be administered with a meal to enhance absorption (bioavailability increases 3-fold when administered with high-fat meal)
Clindamycin (Cleocin)	*Oral solution:* 15mg/mL *Capsules:* 75mg, 150mg, 300mg *Intravenous*	*More frequent:* • Pseudomembranous colitis *Less frequent:* • Hypersensitivity (skin rash, redness, pruritis) • Neutropenia • Thrombocytopenia	• Gastrointestinal disturbances (abdominal pain, nausea, vomiting, diarrhea) • Fungal overgrowth, rectal and genital areas	• Intravenous preparation contains benzyl alcohol, not recommended for use in neonates • Intravenous preparation must be diluted prior to administration • Capsule formulation should be taken with food or a full glass of water to avoid esophageal irritation
Dapsone	*Syrup (compassionate use IND):* 2mg/mL *Tablets:* 25mg, 100mg	*More frequent:* • Hemolytic anemia (especially if G6-PD deficiency) • Methemoglobinemia • Skin rash *Rare:* • Blood dyscrasias • Exfoliative skin disorders (including Stevens-Johnson Syndrome) • Hepatic toxicity • Mood or other mental changes • Peripheral neuritis • Hypersensitivity reaction (fever, rash, jaundice, anemia)	• Central nervous system toxicity (headache, insomnia, nervousness) • Gastrointestinal disturbances (anorexia, nausea, vomiting)	• Protect from light; dispense syrup in amber glass bottles

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Pentamidine (Pentam)	*Intravenous*	*More frequent:* • Nephrotoxicity • Hypoglycemia • Hyperglycemia or diabetes mellitus • Elevated liver transaminases • Hypotension • Leukopenia or neutropenia • Thrombocytopenia *Less frequent:* • Anemia • Cardiac arrhythmias • Hypersensitivity (skin rash, fever) • Pancreatitis • Phebitis • Sterile abscess (at site injection)	*More frequent:* • Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea) *Less frequent:* • Unpleasant metallic taste	• Rapid infusion can results in precipitous hypotension; intravenous infusion should be administered over ≥60 minutes (preferably 2 hours) • Cytolytic effect on pancreatic beta islet cells, leading to insulin release, can result in prolonged severe hypoglycemia (usually occurs after 5 to 7 days therapy, but can also occur after drug discontinued); risk increased with higher dose, longer duration of therapy, and retreatment ≤3 months • Hyperglycemia and diabetes mellitus may occur up to several months after drug discontinued
	Aerosol	*More frequent:* • Sneezing • Cough	*More frequent:* • Bronchospasm	
Primaquine	*Tablets:* 15mg (base)	*More frequent:* • Hemolytic anemia (with G6-PD deficiency) *Less frequent:* • Methemoglobinemia *Rare:* • Leukopenia	• Gastrointestinal disturbances (nausea, vomiting)	• Take with meals or antacids to minimize gastric irritation • Store in light-resistant container

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim, Septra)	*Oral suspension:* TMP 8mg/mL and SMX 40mg/mL *Tablets:* Single strength: TMP 80mg and SMX 400mg Double strength: TMP 160mg and SMX 800mg *Intravenous*	*More frequent:* • Skin rash *Less frequent:* • Hypersensitivity reactions (skin rash, fever) • Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia) *Rare:* • Exfoliative skin disorders (including Stevens-Johnson Syndrome) • Hemolytic anemia (with G6-PD deficiency) • Methemoglobinemia • Renal toxicity (crystalluria, nephritis, tubular necrosis) • Central nervous system toxicity (aseptic meningitis) • Pseudomembranous colitis • Cholestatic hepatitis • Thyroid function disturbance	• Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea)	• Requires dose adjustment in patients with impaired renal function • Maintain adequate fluid intake to prevent crystalluria and stone formation (take with full glass of water) • Potential for photosensitivity skin reaction with sun exposure • Intravenous infusion over 60 to 90 minutes
Anti-Mycobacterial Drugs				
Amikacin	*Intravenous*	*More frequent:* • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Ototoxicity, both auditory and vestibular *Less frequent:* • Hypersensitivity (skin rash, redness or swelling) *Rare:* • Neuromuscular blockade		• Must be infused over 30 to 60 minutes to avoid neuromuscular blockade • Requires dose adjustment in patients with impaired renal function • Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy
Azithromycin (Zithromax)	*Oral suspension:* 20mg/mL, 40mg/mL *Capsules:* 250mg, 600mg *Intravenous*	*More frequent:* • Thrombophlebitis (intravenous form) *Rare:* • Acute interstitial nephritis • Allergic reactions/anaphylaxis (dyspnea, hives, rash) • Pseudomembranous colitis	• Gastrointestinal disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) • Dizziness, headache	• Administer 1 hour before or 2 hours after a meal; do not administer with aluminum- and magnesium-containing antacids • Intravenous: should be infused at concentration of 1mg/mL over a 3 hour period or 2mg/mL over a 1 hour period; should not be administered as a bolus • Use with caution in patients with hepatic function impairment (biliary excretion main route of elimination) • Potential drug interactions

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Capreomycin (Capastat)	*Intramuscular*	*More frequent:* • Nephrotoxicity *Less frequent:* • Hypersensitivity (rash, fever) • Hypokalemia • Neuromuscular blockade • Ototoxicity, both auditory and vestibular • Injection site pain, sterile abscess		• Requires dose adjustment in patients with impaired renal function • Administer only by deep intramuscular injection into large muscle mass (superficial injections may result in sterile abscess) • Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy
Ciprofloxacin (Cipro)	*Oral suspension:* 50mg/mL, 100mg/mL *Tablets:* 100mg, 250mg, 500mg, 750mg *Intravenous*	*More frequent:* • QTc-interval prolongation *Less frequent:* • Phototoxicity *Rare:* • Central nervous system stimulation • Hepatotoxicity • Hypersensitivity reactions (rash, pruritis, exfoliative skin disorders including Stevens-Johnson Syndrome, dyspnea, vasculitis) • Interstitial nephritis • Phlebitis (at injection sites) • Pseudomembranous colitis • Tendonitis or tendon rupture	*More frequent:* • Gastrointestinal disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) • Central nervous system toxicity (dizziness, headache, insomnia, drowsiness) *Less frequent:* • Change in taste • Photosensitivity	• Can be taken without regard to meals • Avoid concurrent antacids or sucralfate (take ≥6 hours before or 2 hours after ciprofloxacin) • Take with full glass of water to avoid crystalluria • Possible phototoxicity reactions with sun exposure • Intravenous infusions should be over 1 hour
Clarithromycin (Biaxin)	*Oral suspension:* 25mg/mL, 50mg/mL *Tablets:* 250mg, 500mg	*Rare:* • Hepatotoxicity • Hypersensitivity reaction (rash, pruritis, dyspnea) • Pseudomembranous colitis • Thrombocytopenia	*Frequent:* • Gastrointestinal disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) *Infrequent:* • Abnormal taste sensation • Headache	• Requires dose adjustment in patients with impaired renal function • Can be administered without regard to meals • Reconstituted suspension should not be refrigerated • Potential drug interactions

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Cycloserine (Seromycin)	*Capsules:* 250mg	*More frequent:* • Central nervous system toxicity (including confusion, anxiety) *Less frequent:* • Hypersensitivity (skin rash) • Peripheral neuropathy • Seizures • Psychosis *Rare:* • Cardiac arrhythmias	• Headache *Rare:* • Photosensitivity	• Take with food to minimize gastric irritation • Neurotoxicity is related to excessive serum concentrations; serum concentrations should be maintained at 25–30mcg/mL • Do not administer to patients with severe renal impairment (due to increased risk of neurotoxicity) • Should monitor serum levels, if possible • Should administer pyridoxine at the same time
Ethambutol (Myambutol)	*Tablets:* 100mg, 400mg	*Infrequent:* • Acute gouty arthritis (secondary to hyperuricemia) *Rare:* • Hypersensitivity (rash, fever, joint pain) • Peripheral neuritis • Retrobulbar optic neuritis	• Gastrointestinal disturbances (abdominal pain, anorexia, nausea, vomiting) • Confusion • Disorientation • Headache	• Requires dose adjustment in patients with impaired renal function • Take with food to minimize gastric irritation • Monitor visual acuity and red-green color discrimination • Avoid concomitant use of drugs with neurotoxicity
Ethionamide (Trecator-SC)	*Tablets:* 250 mg	*Infrequent:* • Hepatitis, jaundice • Peripheral neuritis • Psychiatric disturbances *Rare:* • Goiter or hypothyroidism • Hypoglycemia • Optic neuritis • Skin rash	*More frequent:* • Gastrointestinal disturbances (anorexia, metallic taste, nausea, vomiting, stomatitis) • Orthostatic hypotension *Rare:* • Gynecomastia	• Avoid use of other neurotoxic drugs that could increase potential for peripheral neuropathy and optic neuritis • Administration of pyridoxine may alleviate peripheral neuritis • Take with food to minimize gastric irritation
Isoniazid	*Oral syrup:* 10mg/mL *Tablets:* 50mg, 100mg, 300mg *Intramuscular*	*More frequent:* • Hepatitis prodromal syndrome (anorexia, weakness, vomiting) • Hepatitis • Peripheral neuritis *Rare:* • Blood dyscrasias • Hypersensitivity (fever, rash, joint pain) • Neurotoxicity (includes seizure) • Optic neuritis	• Gastrointestinal disturbances (abdominal pain, nausea, vomiting, diarrhea)	• Take with food to minimize gastric irritation • Take ≥1 hour before aluminum-containing antacids • Hepatitis less common in children • Use with caution in patients with hepatic function impairment, severe renal failure, or history of seizures • Pyridoxine supplementation should be provided for all HIV-infected children

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Kanamycin	*Vials* 75mg/2mL 500mg/2mL 1 gm/3mL *Intramuscular*	*More frequent:* • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Ototoxicity, both auditory and vestibular *Less frequent:* • Hypersensitivity (skin rash, redness or swelling) *Rare:* • Neuromuscular blockade		• Must be infused over 30 to 60 minutes to avoid neuromuscular blockade • Requires dose adjustment in patients with impaired renal function • Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy
P-aminosalicyclic acid	*Delayed release granules*: 4 gm per packet	*Rare:* • Hypersensitivity (fever, skin rash, exfoliative dermatitis, mono-like or lymphoma-like syndrome, jaundice, hepatitis, pericarditis, vasculitis, hematologic abnormalities including hemolytic anemia, hypoglycemia, optic neuritis, encephalopathy, reduction in prothrombin) • Crystalluria • Hemolytic anemia	• Gastrointestinal disturbances (abdominal pain, nausea, vomiting, diarrhea)	• Should not be administered to patients with severe renal disease • Drug should be discontinued at first sign suggesting hypersensitivity reaction (usually rash, fever, gastrointestinal symptoms followed by jaundice) • Vitamin B12 therapy should be considered in patients receiving for >1 month • Administer granules by sprinkling on acidic foods such as apple sauce or yogurt or a fruit drink like tomato or orange juice • Maintain urine at neutral or alkaline pH to avoid crystalluria • The granule soft “skeleton” may be seen in the stool
Pyrazinamide	*Tablets:* 500mg	*More frequent:* • Arthralgia *Less frequent:* • Hepatotoxicity (dose-related) *Rare*: • Acute gouty arthritis secondary to hyperuricemia	• Skin rash, pruritis • Photosensitivity	• Avoid in patients with severe hepatic impairment

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Rifabutin (Mycobutin)	*Capsules:* 150mg	*More frequent:* • Allergic reaction (rash, pruritis) • Gastrointestinal intolerance (anorexia, diarrhea, dyspepsia, nausea, vomiting) • Neutropenia *Less frequent:* • Asthenia *Rare:* • Arthralgia, myalgia • Change in taste • Pseudojaundice • Thrombocytopenia • Uveitis	• Headache • Insomnia	• Preferably take on empty stomach, but may administer with food in patients with gastrointestinal intolerance • Contents of capsules may be mixed with applesauce if unable to swallow capsule • May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses) • Uveitis seen with high dose rifabutin (adults >300mg/day) especially when combined with clarithromycin • Multiple potential drug interactions
Rifampin (Fifadin)	*Oral suspension*: (not commercially available but can be prepared from capsules of 1.2 gm rifampin in 120 mL syrup) *Capsules*: 150mg, 300mg *Intravenous*	*Infrequent:* • "Flu-like" syndrome *Rare:* • Blood dyscrasias • Hepatitis prodromal syndrome (anorexia, nausea, vomiting, weakness) • Hepatitis • Interstitial nephritis	• Gastrointestinal disturbances (abdominal pain, diarrhea)	• Preferably take on empty stomach, but may administer with food in patients with gastrointestinal intolerance; take with full glass of water • Suspension formulation stable for 30 days • May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses) • Multiple potential drug interactions
Streptomycin	*Intramuscular*	*More frequent:* • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Peripheral neuritis • Ototoxicity, both auditory and vestibular *Less frequent:* • Hypersensitivity (skin rash, redness or swelling) • Optic neuritis *Rare:* • Neuromuscular blockade		• Usual route of administration is deep intramuscular injection into large muscle mass • For patients who cannot tolerate intramuscular injections, dilute to 12–15mg in 100 mL of 0.9% sodium chloride; must be infused over 30 to 60 minutes to avoid neuromuscular blockade • Requires dose adjustment in patients with impaired renal function • Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Anti-Viral Drugs				
Acyclovir (Zovirax)	*Oral suspension:* 40mg/mL *Capsules:* 200mg *Tablets:* 400mg, 800mg *Intravenous*	*More frequent:* • Phelbitis (at injection site when given intravenously) *Less frequent:* • Acute renal failure (parenteral use, more common with rapid infusion) *Rare:* *Parenteral form only:* • Encephalopathy • Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia, hemolysis) • Crystalluria, hematuria • Disseminated intravascular coagulation • Hypotension • Neuropsychiatric toxicity (with high doses) *Parenteral and oral forms:* • Rash (urticarial, exfoliative skin disorders including Stevens-Johnson Syndrome) • Anaphylaxis • Seizures • Elevated transaminase enzymes • Fever, hallucinations • Leukopenia • Lymphadenopathy • Peripheral edema • Visual abnormalities	*More frequent:* • Gastrointestinal disturbances (anorexia, diarrhea, nausea, vomiting) • Headache, lightheadness • Malaise *Less frequent (more marked in older adults):* • Agitation • Alopecia • Dizziness • Myalgia, paresthesia • Somnolence	• Requires dose adjustment in patients with renal impairment • Avoid other nephrotoxic drugs • Infusion concentrations of <7mg/mL are recommended • Should be infused slowly over 1 hour to avoid renal tubular damage; must be accompanied by adequate hydration

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Cidofovir (Vistide)	*Intravenous*	*More frequent:* • Nephrotoxicity • Neutropenia *Less frequent:* • Fever *Rare:* • Vision changes due to ocular hypotony	• Gastrointestinal disturbances (anorexia, diarrhea, nausea, vomiting) • Headache • Asthenia	• Infuse over 1 hour • Should not be used in patients with severe renal impairment • Probenecid must be administered prior to each dose of cidofovir and 2 and 8 hours after infusion • Each dose must be administered with 1 liter of 0.9% sodium injection, infused over 1 to 2 hours immediately before cidofovir infusion; if the patient can tolerate the fluid load, a second liter should be started either at the beginning of the cidofovir infusion or immediately afterward • Concurrent use of other nephrotoxic drugs should be avoided
Foscarnet (Foscarvir)	*Intravenous*	*More frequent:* • Nephrotoxicity • Serum electrolyte abnormalities (hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia) *Less frequent:* • Hematologic toxicity (anemia, granulocytopenia) • Neurotoxicity (muscle twitching, tremor, seizures, tingling around mouth) • Cardiac abnormalities secondary to electrolyte changes • Phelbitis (at site of injection) *Rare:* • Sores or ulcers mouth or throat	*Frequent:* • Gastrointestinal disturbances (abdominal pain, anorexia, nausea, vomiting) • Anxiety, confusion, dizziness, headache • Fever	• Requires dose adjustment in patients with impaired renal function • Use adequate hydration to decrease nephrotoxicity • Avoid concomitant use of other drugs with nephrotoxicity • Monitor serum electrolytes • Intravenous solution of 24mg/mL can be administered via central line but must dilute to 12mg/mL if given via peripheral line • Must be administered at a constant rate by infusion pump over ≥2 hours (or no faster than 1 mg/kg/minute)

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Ganciclovir (Cytovene)	*Capsules:* 250mg, 500mg *Intravenous*	*More frequent:* • Granulocytopenia • Thrombocytopenia *Less frequent:* • Anemia • Central nervous system effects (confusion, headache) • Hypersensitivity (fever, rash) • Elevated transaminase enzymes • Increase in creatinine, BUN • Phelbitis (at injection sites) *Rare:* • Retinal detachment • Seizures • Psychosis	• Gastrointestinal disturbances (abdominal pain, anorexia, nausea, vomiting)	• Requires dose adjustment in patients with renal impairment • Avoid other nephrotoxic drugs • Intravenous infusion over 1 hour. In-line filter required. • Maintain good hydration • Undiluted intravenous solution is alkaline (pH 11); use caution in handling and preparing solutions and avoid contact with skin and mucus membranes • Administer oral doses with food to increase absorption
Interferon-alfa	*Parenteral (subcutaneous or intramuscular use)*	*More frequent:* • Hematologic toxicity (leukopenia, thrombocytopenia) • Neurotoxicity (confusion, depression, insomnia, anxiety) • Injection erythema *Less frequent:* • Cardiovascular effects (chest pain, hypertension, arrhythmias) • Hypoesthesia/paresthesia *Rare:* • Abnormality or loss of vision • Allergic reaction (rash, hives) • Hypothyroidism • Development of anti-nuclear antibodies	*More frequent:* • Flu-like syndrome (myalgia, arthralgia, fever, chills, headache, back pain, malaise, fatigue) • Gastrointestinal disturbances (abdominal pain, anorexia, nausea, vomiting, diarrhea, dyspepsia) • Pharyngitis *Infrequent:* • Alopecia • Epistaxis	• Severe adverse effects less common in children than adults • Toxicity dose-related, with significant reduction over the first 4 months of therapy • For non-life threatening reactions, reduce dose or temporarily discontinue drug and restart at low doses with stepwise increases • If patients have visual complaints, ophthalmologic exam should be performed to detect possible retinal hemorrhage or retinal artery or vein obstruction • Should not be used in children with decompenstated hepatic disease, significant cytopenia, autoimmune disease, or significant pre-existing renal or cardiac disease • If symptoms of hepatic decompensation occur (ascites, coagulopathy, jaundice), interferon-alfa should be discontinued

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Lamivudine (Epivir)	*Oral solution:* 10mg/mL *Tablets:* 100mg, 150mg, 300mg (soon available)	*More frequent:* • Pancreatitis • Peripheral neuropathy/paresthesias *Less frequent:* • Hematologic toxicity (anemia, neutropenia) • Skin rash	*Infrequent:* • Gastrointestinal disturbances (abdominal pain, nausea, vomiting) • Headache, insomnia • Dizziness, fatigue • Cough *Rare:* • Hair loss	• Avoid use in patients with history of pancreatitis or peripheral neuropathy • Requires dose adjustment in patients with renal impairment • HIV/HBV-coinfected children should not be treated with lamivudine monotherapy; lamivudine should be given as part of potent combination regimen and the dose used for HIV treatment
Ribavirin	*Inhalation solution:* 6 gm vial (oral solution and intravenous preparation not available commercially but can be prepared by diluting ribavirin inhalation product vial) *Capsules:* 200mg (in kit with interferon-alfa)	• Hemolytic anemia (with associated potential for increase in unconjugated bilirubin and uric acid) *Infrequent:* • Neutropenia	• Central nervous system effects (fatigue, headache, insomnia, depression) • Gastrointestinal disturbances (abdominal pain, nausea, vomiting) • Skin rash	• After reconstitution, ribavirin oral solution stable for 24 hours • Intravenous infusion should be over 15 to 20 minutes • Should not be used in patients with severe renal impairment • Should not be used as monotherapy for treatment of hepatitis C, but used in combination with interferon-alfa • Intracellular phosphorylation of pyrimidine nucleoside analogues (zidovudine, stavudine, zalcitabine) decreased by ribavirin, may have antagonism, use with caution • Enhances phosphorylation of didanosine, use with caution due to increased risk pancreatitis/mitochondrial toxicity
Valacyclovir (Valtrex)	*Tablets:* 500mg, 1 gm (an oral suspension formulation 50mg/mL can be prepared in Ora-Sweet or Syrpalta syrups)	• Dysmenorrhea • Thrombotic microangiopathy (high dose)	*More frequent:* • Headache, nausea *Less frequent:* • Arthralagia • Dizziness, fatigue • Gastrointestinal disturbances (diarrhea or constipation, anorexia, abdominal pain, vomiting)	• An oral suspension formulation can be prepared in Ora-Sweet or Syrpalta syrups (to yield a final concentration of 50mg/mL of the hydrochloride salt); stable for 21 days in amber glass bottles. • Thrombotic thrombocytopenia purpura/hemolytic uremic syndrome has been reported in HIV-infected adults with advanced disease receiving high (8 gm/day) but not lower doses

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Valganciclovir (Valcyte)	*Tablets:* 450mg	*More frequent:* • Granulocytopenia • Thrombocytopenia *Less frequent:* • Anemia • Central nervous system effects • Hypersensitivity (fever, rash) • Elevated transaminase enzymes • Increase in creatinine, BUN	• Gastrointestinal disturbances (abdominal pain, anorexia, nausea, vomiting)	• Requires dose adjustment in patients with renal impairment • Avoid other nephrotoxic drugs • Tablets should not be broken or crushed
Anti-Parasitic Drugs				
Albendazole (Albenza)	*Tablets:* 200mg	*More frequent:* • Abnormal liver function results *Less frequent:* • Hypersensitivity (rash, pruritis) • Neutropenia (with high doses) *Rare:* • Pancytopenia	*Infrequent:* • Central nervous system effects (dizziness, headache) • Gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting) *Rare:* • Alopecia	• Take with meals to increase absorption
Nitazoxanide (Alinia)	*Oral suspension:* 20mg/mL *Tablets (not yet commercially available):* 500mg		• Gastrointestinal disturbances (abdominal pain, nausea, vomiting) • Headache *Rare:* • Yellow sclera	• Should be given with food
Pyrimethamine (Daraprim)	*Tablet:* 25mg	*Less frequent:* • Neutropenia • Thrombocytopenia • Megaloblastic anemia *Rare:* • Stevens-Johnson Syndrome	• Skin rash	• To prevent hematologic toxicity, administer with leucovorin
Sulfadiazine	*Tablet:* 500mg	*Rare:* • Crystalluria, renal failure • Bone marrow suppression/blood dyscrasias • Severe hypersensitivity syndrome	• Gastrointestinal disturbances (abdominal pain, diarrhea, nausea)	• Ensure adequate fluid intake to avoid crystalluria

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Anti-Malarial Drugs				
Primaquine	*Tablets:* 15mg (base)	*More frequent:* • Hemolytic anemia (with G6-PD deficiency) *Less frequent:* • Methemoglobinemia *Rare:* • Leukopenia	• Gastrointestinal disturbances (nausea, vomiting)	• Take with meals or antacids to minimize gastric irritation • Store in light-resistant container
Mefloquine	*Tablets:* 250mg	*More frequent:* • Central nervous system (dizziness, vivid dreams, insomonia)	• Side effects less prominent in children	• No pediatric tablets • Bitter tasting, use with marshmallows can mask taste • Side effects requiring discontinuation ~4%
Atovaquone/ Proguanil	*Tablets:* Pediatric tabs = 62.5mg/25mg Adult tabs = 250mg/100mg	*Less Frequent:* • Vomiting • Pruritic	• Not for severe renal impairment [GFR <30 mL/min]	• Pediatric tablets available making dosing easier • In adults, side effects similar to placebo • Side effects requiring discontinuation ~1%–2%
Doxycycline	*Tablets:* 50mg, 75mg, & 100mg tablets and capsules *Suspension:* a 25mg/5 mL oral suspension and a 50mg/5 ml syrup	*More frequent:* • GI irritation, pill esophagitis • Photo sensitivity	• Staining of teeth, use in persons >8 years • Photoonycholysis	• Swallow with adequate amounts of fluids • Milk decreases mean absorption by 30% • Provides rickettsial and leptospirosis prophylaxis
Chloroquine Phosphate	*Tablets:* 500mg 250mg	*More frequent:* • Pruritis: Common in persons of African descent (25%–33%)	• Psoriasis exacerbations	• Well tolerated at prophylaxis dosing • Store in child-proof containers • Can be toxic in overdose • Bitter tasting • Solution available worldwide, but not in United States
Quinidine	*Intravenous*	*Serious:* • Cardiac arrhythmias • Hypoglycemia	*Very Frequent:* • Cinchonism: dose dependent effect with tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium • Nausea, diarrhea	• EKG monitoring is standard of care • Do not give by bolus infusion • If EKG changes observed, slow infusion rate

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	**Indicating need for medical attention if persistent or bothersome**	
Artesunate	*Intravenous* (available from CDC Malaria Hotline only; telephone: 770-488-7788)			• ~40% less mortality than with quinidine use in severe malaria • 50% less hypoglycemia than quinidine
Anti-Bacterial Drugs (Note: clarithromycin and azithromycin are listed under anti-mycobacterial drugs)				
Doxycycline	*Capsules:* 20mg, 50mg, 75mg, 100mg *Tablet:* 20mg, 50mg, 100mg *Syrup:* 50mg/5 mL (60 mL) *Suspension*: 25mg/5 mL (60 mL) *Injection*: 100mg, 200mg	*Uncommon:* • May cause increased intracranial pressure, photosensitivity, hemolytic anemia, rash, and hypersensitivity reactions	• Gastrointestinal disturbances (nausea, vomiting, abdominal cramps)	• Use with caution in hepatic and renal disease • Intravenous doses should be infused over 1 to 4 hours • Patient should avoid prolonged exposure to direct sunlight (skin sensitivity) • Generally not recommended for use in children <8 years of age owing to risk for tooth enamel hypoplasia and discoloration, unless benefit outweighs the risk

Drug	Preparations	Major Toxicities*		Special Instructions
		Indicating need for medical attention	Indicating need for medical attention if persistent or bothersome	
Erythromycin	Erythromycin base *Tablet:* 250mg, 333mg, 500mg *Delayed-release tablet:* 250mg, 333mg, 500mg *Delayed-release capsule*: 250mg Erythromycin ethyl succinate *Suspension:* 200mg, 400mg/5 mL (100, 480 mL) *Oral drops:* 100mg/2.5 mL *Chewable tablet:* 200mg *Tablet:* 400mg Erythromycin estolate *Suspension:* 125mg, 250mg/5 mL Erythromycin stearate *Tablet:* 250mg, 500mg Erythromycin gluceptate *Injection:* 1,000mg Erythromycin lactobionate *Injection:* 500mg, 1,000mg	*Uncommon:* • Estolate may cause cholestatic jaundice, although hepatotoxicity is uncommon (2% of reported cases).	• Gastrointestinal disturbances (nausea, vomiting, abdominal cramps)	• Use with caution in liver disease • Oral therapy should replace intravenous therapy as soon as possible • Give oral doses after meals • Parenteral administration should consist of a continuous drip or slow infusion over 60 minutes or longer • Adjust dose in renal failure • Erythromycin should be used with caution in neonates; hypertrophic pyloric stenosis and life-threatening episodes of ventricular tachycardia associated with prolonged QTc interval have been reported • High potential for interaction with many antiretrovirals and other drugs

* The toxicities listed in the table have been selected based on their potential clinical significance and are not inclusive of all side effects reported for a particular drug.

TABLE 6. Drug Interactions of Clinical Significance*

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Anti-Fungal Drugs			
Amphotericin B Amphotericin B lipid complex (Abelcet) Amphotericin B liposome (AmBisome)		Potential for increased toxicity due to overlapping toxicity or side effect of amphotericin (e.g., hypokalemia): ***Bone marrow suppressant drugs:*** Corticosteroids, corticotropin *Cardiovascular drugs:* digitalis glycosides *Diuretics:* potassium depleting *Nephrotoxic drugs* *Neuromuscular blocking drugs*	
Caspofungin		Decreases caspofungin levels: *Anticonvulsant drugs:* phenytoin *Antimycobacterial drugs:* rifampin *Antiretroviral drugs:* efavirenz, nevirapine, nelfinavir	Increases concomitant drug levels: *Anticancer:* tacrolimus
Flucytosine		Increases flucytosine levels: *Nephrotoxic drugs*: (medications that impair glomerular filtration)	
Ketoconazole	Decreases ketoconazole levels: *Antiretroviral drugs:* nevirapine Increases concomitant drug levels: *Antihistamines:* astemizole, terfenadine *Gastrointestinal drugs:* cisapride *Sedative/hypnotics:* midazolam, triazolam	Decreases ketoconazole levels: *Anticonvulsant drugs:* phenytoin *Antimycobacterial drugs:* isoniazid, rifampin Decreases ketoconazole absorption: *Antiretroviral drugs:* didanosine *Gastrointestinal drugs:* antacids, anticholinergics/ antispasmodics, histamine H_2-receptor antagonists, omeprazole, sucralfate *Minerals:* ferrous sulfate, zinc Potential for increased toxicity due to overlapping toxicity: *Hepatotoxic drugs*	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Anticonvulsant drugs:* phenytoin *Antiretroviral drugs:* indinavir *Cardiovascular drugs:* digoxin *Immunosuppressant drugs:* cyclosporine
Fluconazole	Increases concomitant drug levels: *Antihistamines:* terfenadine (with high dose fluconazole) *Gastrointestinal drugs:* cisapride	Decreases fluconazole levels: *Anticonvulsant drugs:* phenytoin *Antimycobacterial drugs:* rifampin Increases concomitant drug levels: *Antidiabetic drugs:* oral agents *Antimycobacterial drugs:* rifabutin *Antidepressant drugs*: amitriptyline	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Anticonvulsant drugs:* phenytoin *Asthma drugs:* theophylline *Immunosuppressant drugs:* cyclosporin (with high dose fluconazole) *Sedative/hypnotics:* midazolam

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Itraconazole	Increases concomitant drug levels: *Antihistamines:* astemizole, terfenadine *Gastrointestinal drugs:* cisapride *Sedative/hypnotics:* midazolam, triazolam *Statins:* lovastatin, simvastatin	Decreases itraconazole levels: *Anticonvulsant drugs:* carbamazepine, phenytoin *Antimycobacterial drugs:* rifampin Decreases itraconazole absorption: *Antiretroviral drugs:* didanosine *Gastrointestinal drugs:* antacids, anticholinergics/ antispasmodics, histamine H_2-receptor antagonists, omeprazole, sucralfate *Minerals:* ferrous sulfate, zinc Increases concomitant drug levels: *Antidiabetic drugs:* oral agents	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Anticonvulsant drugs:* carbamazepine, phenytoin *Cardiovascular drugs:* digoxin *Immunosuppressant drugs:* cyclosporin
Posaconazole	Increases posaconzaole levels: *Antihistamines:* astemizole, terfenadine *Antimalarial:* Halofantrine *Cardiovascular drugs*: quinidine *Ergot alkaloids*: ergotamine, dihydroergotamine *Gastrointestinal drugs*: cisapride *Psychiatric drugs*: pimozide	May decrease posaconazole drug levels *(*avoid concomitant use unless benefit outweighs the risks): *Anticonvulsant drugs:* phenytoin *Antimycobacterial drugs:* rifabutin *Gastrointestinal drugs:* cimetidine May increase concomitant drug levels: *Anticonvulsant drugs:* phenytoin *Antihypertensives (Calcium Channel Blockers metabolized through CYP3A4):*verapamil, diltiazem *Antimycobacterial drugs*: rifabutin *Chemotherapeutic drugs (i.e., vinca alkaloids):* vincristine and vinblastin *Immunosuppressant drugs:* cyclosporin, sirolimus, tacrolimus *Sedative/hypnotics:* midazolam *Statins:* (those metabolized by CYP34A) Increased blood glucose levels with concomitant drug use; requires glucose monitoring: *Diabetic drugs:* glipizide	May increase concomitant drug levels: *Anticonvulsant drugs:* phenytoin *Amtihypertensives (Calcium Channel Blockers metabolized through CYP3A4):* verapamil, diltiazem *Antimycobacterial drugs*: rifabutin *Chemotherapeutic drugs (i.e., vinca alkaloids):* vincristine and vinblastin *Immunosuppressant drugs:* cyclosporin, sirolimus,tacrolimus, *Sedative/hypnotics:* midazolam *Statins:* (those metabolized by CYP34A)

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Voriconazole	Decreases voriconazole levels: *Anticonvulsant drugs:* carbamazepine, long-acting barbiturates *Antimycobacterial drugs:* rifabutin, rifampin Increases concomitant drug levels: *Antihistamines:* astemizole, terfenadine *Antimycobacterial drugs:* rifabutin *Cardiovascular drugs:* quinidine *Ergot alkaloids* *Gastrointestinal drugs:* cisapride *Immunosuppressant drugs:* sirolimus *Psychiatric drugs:* pimozide	Increases voriconazole levels: *Antiretroviral drugs:* amprenavir, ritonavir, saquinavir May increase or decrease voriconazole levels: *Antiretroviral drugs:* delavirdine, efavirenz Increases concomitant drug levels: *Antiretroviral drugs:* amprenavir, nelfinavir, saquinavir, delavirdine *Antidiabetic drugs:* oral *Statins*	Increases concomitant drug levels: *Anticancer drugs:* vinca alkaloids *Anticoagulant drugs:* warfarin, coumarin derivatives *Anticonvulsant drugs:* phenytoin *Cardiovascular drugs:* felodipine (calcium channel blockers) *Gastrointestinal drugs drugs:* omeprazole *Immunosuppressant drugs:* cyclosporin, tacrolimus *Sedative/hypnotics:* midazolam, triazolam, alprazolam *Statins:* lovastatin, simvastatin Decreases voriconazole levels: *Anticonvulsant drugs:* phenytoin
Anti-Pneumocystis Drugs			
Atovaquone	Decreases atovoquone levels: *Antimycobacterial drugs:* rifampin	Decreases atovaquone levels: *Antimycobacterial drugs:* rifabutin	
Clindamycin	Decreases clindamycin antibacterial efficacy: *Antibacterial drugs:* chloramphenicol, erythromycins	Increases concomitant drug toxicity: *Anesthetics:* hydrocarbon inhalation *Neuromuscular blocking drugs*	
Dapsone		Increases dapsone levels: Probenecid Decreases dapsone levels: *Antimycobacterial drugs:* rifampin Decreases dapsone absorption: *Antiretroviral drugs:* didanosine Increases levels both drugs: *Antibacterial drugs:* trimethoprim Potential for increased toxicity due to overlapping toxicity: *Bone marrow suppressant drugs or drugs associated with hemolysis*	
Pentamidine	Potential for increased toxicity due to overlapping toxicity: *Anti-emetic drugs:* droperidol *Antiretroviral drugs:* zalcitibine	Potential for increased toxicity due to overlapping toxicity: *Antiviral drugs:* foscarnet *Antiretroviral drugs:* didanosine *Bone marrow suppressant drugs* *Nephrotoxic drugs*	

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Primaquine	Potential for increased toxicity due to overlapping toxicity: *Antiprotozoal drugs:* quinacrine	Potential for increased toxicity due to overlapping toxicity: *Bone marrow suppressant drugs or drugs associated with hemolysis* *Nephrotoxic drugs*	
Trimethoprim-sulfamethoxazole	Potential for increased toxicity due to overlapping toxicity: *Folate antagonists*	Decreases trimethoprim levels: *Antimycobacterial drugs:* rifampin Increases levels both drugs: *Antibacteria drugsl:* dapsone Potential for increased toxicity due to overlapping toxicity: *Bone marrow suppressant drugs*	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Anticonvulsant drugs:* phenytoin *Cardiovascular drugs:* procainamide
Anti-Mycobacterial Drugs			
Amikacin	Potential for increased toxicity due to overlapping toxicity: *Antimycobacterial drugs:* capreomycin	Potential for increased toxicity due to overlapping toxicity: *anti-tuberculosis drugs (injectable):* streptomycin , kanamycin *Nephrotoxic drugs* *Neuromuscular blocking drugs* *Ototoxic drug:* loop diuretics	
Azithromycin		Decreases azithromycin absorption: *Gastrointestinal drugs:* antacids Increases concomitant drug levels: *Antihistamines:* terfenadine *Ergot derivatives* *Sedative/hypnotics:* triazolam	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Anticonvulsant drugs:* carbamazepine, phenytoin *Asthma drugs:* theophylline *Cardiovascular drugs:* digoxin *Immunosuppressant drugs:* cyclosporin
Capreomycin	Potential for increased toxicity due to overlapping toxicity: *Antibacterial drugs:* aminoglycosides (parenteral)	Potential for increased toxicity due to overlapping toxicity: *Nephrotoxic drugs* *Neuromuscular blocking drugs* *Ototoxic drugs:* loop diuretics	
Ciprofloxacin		Increases ciprofloxacin levels: Probenecid Decreases ciprofloxacin absorption: *Antiretroviral drugs:* didanosine *Minerals:* ferrous sulfate, zinc *Gastrointestinal drugs:* antacids, sucralfate, magnesium-containing laxatives Potential increased toxicity concomitant drug: *Antidiabetic drugs:* sulfonylurea (glucose abnormalities, both hypo- and hyper-glycemia, mechanism unclear)	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin *Asthma drugs:* aminophylline, oxtriphylline, theophylline *Immunosuppressant drugs:* cyclosporin Decreases concomitant drug levels: *Anticonvulsant drugs:* phenytoin

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Clarithromycin	Increases concomitant drug levels: *Antihistamines:* astemizole, terfenadine *Gastrointestinal drugs:* cisapride *Psychiatric drugs:* pimozide Potential for increased toxicity due to overlapping toxicity: *Anti-emetic drugs:* droperidol	Decreases clarithromycin levels: *Antimycobacterial drugs:* rifabutin, rifampin *Antiretroviral drugs:* zidovudine	Increases concomitant drug levels: *Anticoagulant drugs:* warfarin, coumadin derivatives *Anticonvulsant drugs:* carbamazapine *Cardiovascular drugs:* digoxin *Asthma drugs:* theophylline
Cycloserine		Potential for increased toxicity due to overlapping toxicity: *Antimycobacterial drugs*: ethionamide, isoniazid	Increases concomitant drug levels: *Anticonvulsant drugs:* phenytoin
Ethambutol		Potential for increased toxicity due to overlapping toxicity: *Neurotoxic drugs*	
Ethionamide		Potential for increased toxicity due to overlapping toxicity: *Neurotoxic drugs* *Antimycobacterial drugs*: cycloserine, isoniazid	Increases concomitant drug levels: *Immunosuppressant drugs:* cyclosporin
Isoniazid		Decreases isoniazid levels: *Corticosteriods*: glucocorticoids (e.g., prednisolone) Decreases isoniazid absorption: *Gastrointestinal drugs:* antacids Increases concomitant drug levels: *Anesthetics:* alfentanil Decreases concomitant drug levels: *Antifungal drugs:* ketoconazole Potential for increased toxicity due to overlapping toxicity: *Antimycobacterial drugs:* rifampin, cycloserine, ethionamide *Hepatotoxic drugs* ***Neurotoxic drugs***	Increases concomitant drug levels: *Anticoagulant drugs:* coumadin derivatives *Anticonvulsant drugs:* carbamazepine, phenytoin *Asthma drugs:* theophylline *Sedative-hypnotics:* benzodiazepines
Kanamycin	Potential for increased toxicity due to overlapping toxicity: *Aminoglycosides:* history of hypersensitivity or toxic reaction to any aminoglycoside *Diuretics(potent):* ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, or mannitol (note: should not be given concurrently)	Potential for increased toxicity due to overlapping toxicity (should be avoided): *Aminoglycosides*: all, including paromomycin *Nephrotoxic and/or neurotoxic drugs:* polymyxin B, bacitracin, colistin, amphotercin B, cisplatin, vancomycin Decreases kanamycin levels: *Beta-lactam-type antibiotics:* penicillins or cephalosporins	

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Pyrazinamide		Potential for increased toxicity due to overlapping toxicity: *Antimycobacterial drugs:* rifampin *Hepatotoxic drugs*	Decreases concomitant drug levels: *Immunosuppressant drugs:* cyclosporine
Rifabutin	Decreases concomitant drug levels: *Antiretroviral drugs:* delavirdine, saquinavir (hard gel capsule without higher dose ritonavir boosting)	Decreases concomitant drug levels: *Antibacterial drugs:* dapsone *Antifungal drugs:* azoles (except for fluconazole) *Cardiovascular drugs:* quinidine, verapamil (oral) *Contraceptives:* oral ***Corticosteriods***	Increases rifabutin levels: *Antiretroviral drugs:* nevirapine; amprenavir, indinavir, nelfinavir, ritonavir, saquinavir in combination with higher dose ritonavir boost Decreases rifabutin levels: *Antiretroviral drugs:* efavirenz Decreases concomitant drug levels: *Antibacterial drugs:* chloramphenicol, dapsone *Anticonvulsant drugs:* barbiturates, diazepam *Antidiabetic drugs:* oral *Anti-lipid drugs:* clofibrate *Antiretroviral drugs:* nevirapine, efavirenz, amprenavir, indinavir, nelfinavir, saquinavir (soft gel cap) *Asthma drugs:* aminophylline, oxtriphylline, theophylline *Cardiovascular drugs:* beta-adrenergic blockers, digitalis glycosides, quinidine, verapamil (oral) *Immunosuppressant drugs:* cyclosporine
Rifampin	Decreases concomitant drug levels: *Contraceptives:* oral *Antiretroviral drugs:* delavirdine, amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir (hard or soft gel without higher dose ritonavir boosting), or dual protease low-dose ritonavir-boosted regimens	Decreases rifampin absorption: *Antimycobacterial drugs:* clofazamine Decreases concomitant drug levels: *Antibacterial drugs:* dapsone, trimethoprim *Antiretroviral drugs:* nevirapine (use only if other options not available and close virologic and immunologic monitoring can be done) *Antifungal drugs:* azoles *Corticosteriods* *Methadone* Potential for increased toxicity due to overlapping toxicity: *Bone marrow suppressant drugs* *Antimycobacterial drugs:* isoniazid, pyrazinamide *Hepatotoxic **drugs***	Decreases concomitant drug levels: *Antibacterial drugs:* chloramphenicol *Anticoagulant drugs:* warfarin, coumadin derivatives *Anticonvulsant drugs:* barbiturates, diazepam, phenytoin *Antidiabetic drugs:* oral *Anti-lipid drugs:* clofibrate *Asthma drugs:* aminophylline, oxtriphylline, theophylline *Cardiovascular drugs:* beta-adrenergic blockers, digitalis glycosides, disopyramide, mexiletine, propafenone, quinidine, tocainide, verapamil (oral) *Immuosuppressant drugs:* cyclosporine *Methadone*
Streptomycin	Potential for increased toxicity due to overlapping toxicity: *Antimycobacterial drugs:* capreomycin	Potential for increased toxicity due to overlapping toxicity: *Nephrotoxic drugs* *Neuromuscular blocking drugs* *Ototoxic drugs*	

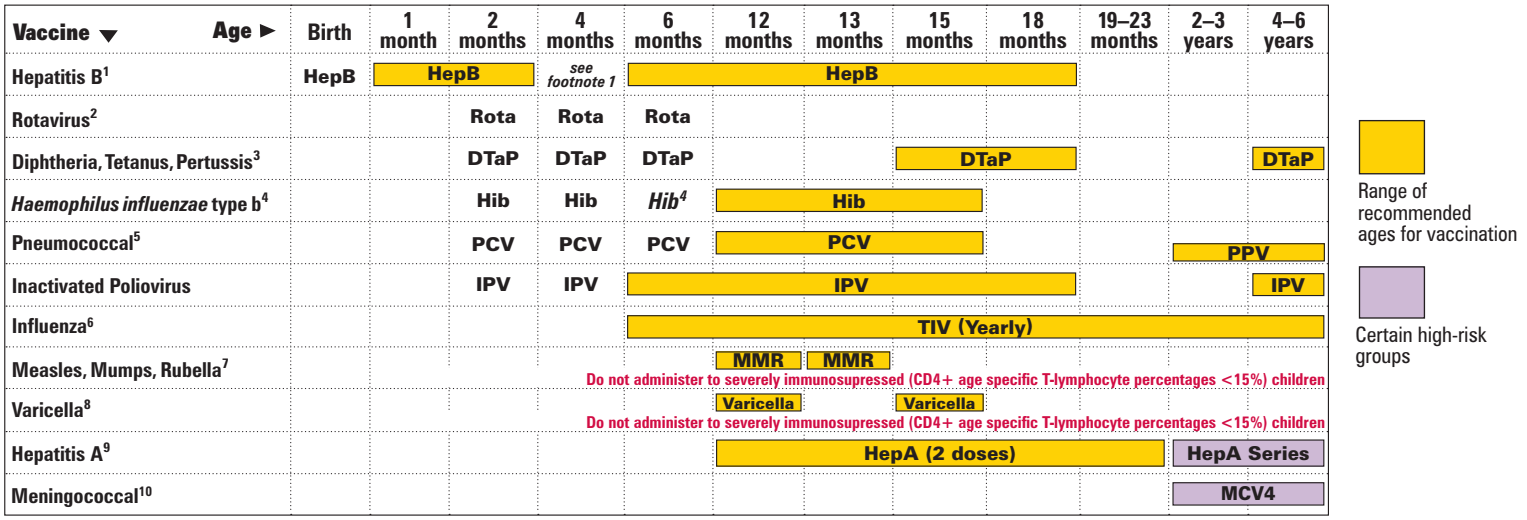
Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Anti-Viral Drugs			
Acyclovir (Valacyclovir)		Increases acyclovir levels: Probenecid Potential for increased toxicity due to overlapping toxicity: *Nephrotoxic drugs*	
Cidofovir	Potential for increased toxicity due to overlapping toxicity: *Antibacterial drugs:* aminoglycosides *Nephrotoxic drugs*		
Foscarnet	Potential for increased toxicity due to overlapping toxicity: *Anesthetic adjuncts:* droperidol *Antiviral drugs:* cidofovir *Anti-pneumocystis drugs*: pentamidine	Potential for increased toxicity due to overlapping toxicity: *Nephrotoxic drugs*	
Ganciclovir (Valganciclovir)		Increases ganciclovir levels: Probenecid Increases concomitant drug levels: *Antiretroviral drugs:* didanosine Potential for increased toxicity due to overlapping toxicity or other mechanisms: *Antibacterial drugs:* impenem-cilastatin *Antiretroviral drugs:* zidovudine *Bone marrow suppressant drugs* *Nephrotoxic drugs*	
Interferon-alfa		Potential for increased toxicity due to overlapping toxicity: *Antiretroviral drugs:* zidovudine *Bone marrow suppressant drugs*	Increases concomitant drug levels: *Asthma drugs:* theophylline *Sedative drugs:* barbiturates
Ribavirin		Increases concomitant level of active drug (potential for increased risk pancreatitis and mitochondrial toxicity): *Antiretroviral drugs:* didanosine Decreases concomitant level of active drug: *Antiretroviral drugs:* zidovudine, stavudine, zalcitabine	

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Anti-Parasitic Drugs			
Albendazole		Increases albendazole levels: *Gastrointestinal drugs:* cimetidine *Corticosteroids* *Anithelminhic drugs:* praziquantel	Decreases concomitant drug levels: *Asthma drugs:* theophylline
Nitazoxanide		Potential for toxicity if concomitant use of highly protein bound drugs with narrow therapeutic index, due to high (>99.9%) protein binding	
Paromomycin		Potential for increased toxicity due to overlapping toxicity: *Neuromuscular blocking drugs*	Decreases concomitant drug levels: *Cardiovascular drugs:* digoxin
Anti-Malarial Drugs			
Atovaquone/Proguanil	Decreases atovaquone levels *Antibacterial drugs*: tetracycline *Antimycobacterial drugs*: rifampin, rifabutin	Increases concomitant drug levels: *Antiretroviral drugs:* zidovudine	
Mefloquine	None	Decreases concomitant drug levels *Antiretroviral drugs:* Ritonavir (decreased ritonavir trough and area under curve)	
Artesunate	None	None	
Quinidine	Ritonavir Other protease inhibitors (generally contraindicated, but in presence of life threatening, severe malaria and in the absence of other therapy, quinidine should be given initially while artesunate is obtained from the CDC)	Increases quinidine levels (may increase probability of arrthymia) *Antiretroviral drugs:* Ritonavir	
Chloroquine	None	None	
Primaquine	None	Potential for increased toxicity Glucose-6-phosphate dehydrogenase oxidative drug use	

Drug Class and Name	Contraindicated Drugs	Drugs that Should be Used with Caution	Drugs that Require Plasma Level Monitoring and/or Dose Adjustment
Anti-Bacterial Drugs (Note: clarithromycin and azithromycin are listed under anti-mycobacterial drugs)			
Doxycycline		Increases doxycycline clearance: *Anticonvulsant drugs:* phenytoin, carbamazepine *Antimycobacterial drugs:* rifampin Potential for increased toxicity of concomitant drug: *Antithrombotic drugs:* warfarin	
Erythromycin	*Gastroinetestinal drugs:* cisapride	Increases concomitant drug levels: *Anticonvulsants:* carbamazepine, clozapine *Anti-inflammtory drugs:* cyclosporine, methylprednisolone *Asthma drugs:* theophylline *Cardiac drugs:* digoxin	

*The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label for complete information on drug interactions).

Recommended Immunization Schedule for HIV-Exposed and Infected Children Aged 0–6 Years—UNITED STATES, 2008



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of January 1, 2008, for **HIV infected children aged 0–6 years**. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended after this immunization schedule is published. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at **http://www.vaers, hhs.gov** or by telephone, **800-822-7967**.

FOOTNOTES

1. Hepatitis B vaccine (HepB). *(Minimum age: birth)*

At birth:
- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine the HBsAg status as soon as possible and if HBsAg-positive, administer HBIG (no later than age 1 week).
- If mother is HBsAg-negative, the birth dose can only be delayed with physician's order and mother's negative HBsAg laboratory report documented in the infant's medical record.

After the birth dose:
- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1–2 months. The final dose should be administered at age ≥24 weeks. Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of ≥3 doses of a licensed HepB series, at age 9–18 months (generally at the next well-child visit).

4-month dose:
- It is permissible to administer 4 doses of HepB when combination vaccines are administered after the birth dose. If monovalent HepB is used for doses after the birth dose, a dose at age 4 months is not needed.

Post vaccination:
- Testing is recommended for HIV-infected children and should be performed 1–2 months after administration of the last dose of the vaccine series using a method that allows determination of a protective level of anti-HBs (≥10mIU/mL).
- Persons found to have anti-HBs levels of <10 mIU/mL after the primary series should be revaccinated. Administration of 3 doses on an appropriate schedule followed by anti-HBs testing 1–2 months after the 3rd dose is usually more practical than serologic testing after one or more doses of vaccine.

Booster dose:
- In HIV infected children, the need for booster doses has not been determined. Annual antiHBs testing and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in persons with ongoing risk of exposure. See *MMWR* 2005:54 [No. RR-16]:1–23.

2. Rotavirus vaccine (Rota). *(Minimum age: 6 weeks)*

No safety or efficacy data are available for the administration of rotavirus vaccine to infants who are potentially immunocompromised, including those who are HIV-positive. However, the following considerations support vaccination of HIV exposed or infected infants: 1) the HIV diagnosis may not be established in infants born to HIV positive mothers before the age of the first rotavirus vaccine dose; only 1.5%–3% of HIV exposed infants in the US will eventually test HIV positive, and 2) Rotateq vaccine is considerably attenuated.
- Administer the first dose at age 6–12 weeks. Do not start the series later than age 12 weeks.
- Administer the final dose in the series by age 32 weeks. Do not administer a dose later than age 32 weeks.
- Data on safety and efficacy outside of these age ranges are insufficient.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). *(Minimum age: 6 weeks)*
- The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4–6 years.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib). *(Minimum age: 6 weeks)*
- If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required.
- TriHiBit® (DTaP/Hib) combination products should not be used for primary immunization but can be used as boosters following any Hib vaccine in children aged ≥12 months.
- Clinicians and other health-care providers might consider use of Hib vaccine among children with HIV infection older than 59 months who did not receive the vaccine as an infant or in childhood. See *MMWR* 2006:55 [No. RR-15]:1–48.

5. Pneumococcal vaccine. *(Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPV])*
- Heptavalent pneumococcal conjugate vaccine (PCV) is recommended for all HIV-infected children aged 2–59 months. Children ≤23 months should be vaccinated according to the routine PCV schedule. For dosing intervals for children starting the vaccination schedule after age 2 months, see *MMWR* 2000;49 [No. RR-9]:1–35. For incompletely vaccinated children aged 24–59 months, administer two doses of PCV at least 8 weeks apart. Children who have previously received three PCV7 doses need only one dose.
- Administering PCV7 to HIV-infected children ≥5 years is not contraindicated.
- Children aged ≥2 years should also receive the 23-valent pneumococcal polysaccharide vaccine (PPV) ≥2 months after their last PCV dose with a single revaccination with the 23-valent vaccine 3–5 years later.

6. Influenza vaccine. *(Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV])*
- All HIV infected children aged 6 months through 6 years and close contacts (including household members) of these children are recommended to receive influenza vaccine each year. Only TIV should be used for HIV-infected children.
- For healthy close contacts aged 2–49 years, live, attenuated influenza vaccine (LAIV) may be used as an alternative to TIV.
- Children receiving TIV should receive 0.25 mL if aged 6–35 months or 0.5 mL if aged ≥3 years.
- Administer 2 doses (separated by ≥4 weeks) for children aged <9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time last season, but only received one dose. See *MMWR* 2007;56 [No. RR-6]:1–54.

7. Measles, mumps, and rubella vaccine (MMR). *(Minimum age: 12 months)*
- MMR vaccine is recommended for all asymptomatic HIV-infected children who are not severely immunosuppressed (CD4+ age specific T-lymphocyte percentages ≥15%) and who lack evidence of measles immunity.
- MMR vaccine for symptomatic HIV-infected children should be considered if they a) do not have evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages ≥15%) and b) lack evidence of measles immunity.
- The first dose of MMR vaccine should be administered as soon as possible after the first birthday. Consideration should be given to administering the second dose 1 month (i.e., a minimum of 28 days) after the first dose rather then waiting until age 4 to 6 years.
- MMRV vaccine has not been studied in HIV infected children and should not be substituted for MMR vaccine.
- MMR and other measles-containing vaccines are not recommended for HIV-infected children with evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages <15%). See *MMWR* 1998;47 [No. RR-8]:1–67, Table 2: Special Considerations for Vaccination—Persons Infected with Human Immunodeficiency Virus [HIV]).

8. Varicella vaccine. *(Minimum age: 12 months)*

Limited data are available on safety and immunogenicity of varicella vaccine in HIV infected children 1–8 years in CDC immunological categories 1 and 2 (CD4+ age specific T-lymphocyte percentages ≥15%) and clinical categories N, A and B.
- Single antigen varicella vaccine should be considered for HIV-infected children with CD4+ age specific T-lymphocyte percentages ≥15%. Eligible children should receive 2 doses 3 months apart with the first dose administered as soon as possible after the first birthday.
- MMRV vaccine has not been studied in HIV infected children and should not be substituted for single antigen varicella vaccine.
- Varicella vaccine is not recommended for HIV-infected children with evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages <15%). See *MMWR*, 2007;56 [No. RR-4]:1–40.

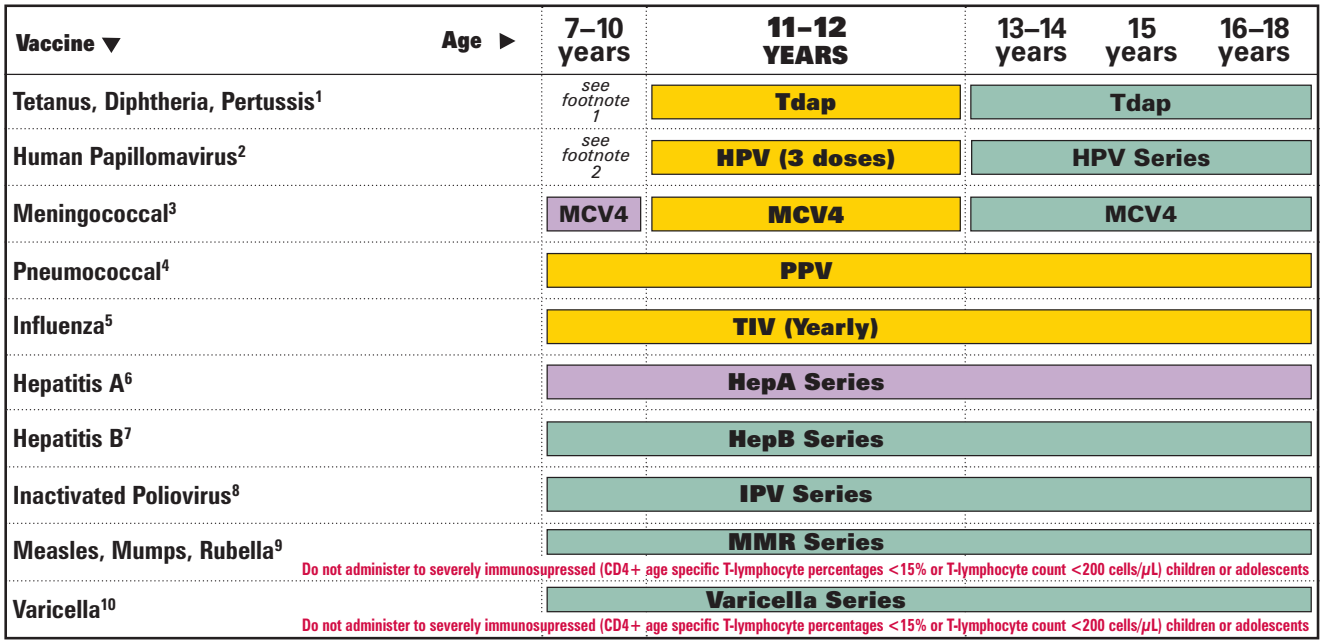
9. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*
- HepA is recommended for all children aged 1 year (i.e., aged 12–23 months). The 2 doses in the series should be administered at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA is recommended for certain other groups of children including in areas where vaccination programs target older children. See *MMWR* 2006;55 [No. RR-7]:1–23.

10. Meningococcal vaccine. *(Minimum age: 2 years for meningococcal conjugate vaccine [MCV4] and for meningococcal polysaccharide vaccine [MPSV4])*
- Administer MCV4 to children aged 2–6 years with terminal complement deficiencies or anatomic or functional asplenia and certain high risk groups.
- Children with HIV are likely at increased risk for meningococcal disease although not to the extent that they are at risk for invasive *S. pneumoniae* infection. Although the efficacy of MCV4 among HIV-infected children is unknown, HIV-infected children that do not fit into the above groups may elect vaccination. See *MMWR* 2005;54 [No. RR-7]:1–21.
- Revaccination with MCV4 is indicated for children vaccinated ≥3 years previously with MPSV4.

FOR MORE INFORMATION SEE THE CATCH-UP SCHEDULE

CS116452

Recommended Immunization Schedule for HIV-Infected Children Aged 7–18 Years—UNITED STATES, 2008



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of January 1, 2008, for **HIV infected children and adolescents aged 7–18 years**. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended after this immunization schedule is published. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at **http://www.vaers, hhs.gov** or by telephone, **800-822-7967**.

FOOTNOTES

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). *(Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL™)*
- Administer at age 11–12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoids vaccine (Td) booster dose.
- Adolescents aged 13–18 years who missed the 11–12 year Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series.

2. Human papillomavirus vaccine (HPV). *(Minimum age: 9 years, females only)*
No data are available on immunogenicity, safety and efficacy of HPV vaccine in HIV-infected females. However, because quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications including HIV-infected females. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent. See *MMWR* 2007;56 [No. RR-2]:1–24 and *MMWR* 2006;55 [No. RR-15]:1–48. Studies are ongoing in HIV infected females.
- Administer the first dose of the HPV vaccine series to females at age 11–12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose.
- Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated.

3. Meningococcal vaccine. *(Minimum age: 2 years for meningococcal conjugate vaccine [MCV4]; 2 years for meningococcal polysaccharide vaccine [MPSV4])*
- Administer MCV4 at age 11–12 years and at age 13–18 years if not previously vaccinated.
- Administer MCV4 to previously unvaccinated college freshmen living in dormitories; MPSV4 is an acceptable alternative.
- Administer MCV4 to children 7–10 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high-risk groups. Revaccination with MCV4 is indicated for children vaccinated ≥3 years previously with MPSV4. See *MMWR* 2005;54 [No. RR-7]:1–21.
- Patients with HIV are likely at increased risk for meningococcal disease although not to the extent that they are at risk for invasive *S. pneumoniae* infection. Although the efficacy of MCV4 among HIV-infected patients is unknown, HIV-infected patients 7–10 years that do not fit into the above groups may elect vaccination.
- For persons 11–18 years who have been previously vaccinated with MPSV4, revaccination with MCV4 is not indicated unless vaccination occurred 3–5 years previously and the person still remains at increased risk for meningococcal disease. For revaccination recommendations. See *MMWR* 2005;54 [No. RR-7]:1–21.

4. Pneumococcal polysaccharide vaccine (PPV). *(Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPV])*
- If not previously vaccinated, children and adolescents aged 7-18 years should receive the 23-valent pneumococcal polysaccharide vaccine; a single revaccination with the 23-valent vaccine should be offered after 3-5 years (children ≤ 10 years) and after 5 years (children >10 years). See *MMWR* 1997;46 [No. RR-8]:1–24, and *MMWR* 2000;49 [No. RR-9]:1–35.
- Administering PCV7 to HIV-infected children ≥5 years is not contraindicated.

5. Influenza vaccine. *(Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV])*
- Influenza vaccine is recommended annually for HIV-infected children and adolescents 7–18 years and their close contacts (including household members). Only TIV should be used for HIV-infected persons.
- For healthy close contacts aged 2–49 years, live, attenuated influenza vaccine (LAIV) may be used as an alternative to TIV.
- Administer 2 doses (separated by 4 weeks or longer) to children aged <9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time last season but only received one dose. See *MMWR* 2007;56 [No. RR-6]:1–54.

6. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*
- The 2 doses in the series should be administered at least 6 months apart.
- HepA is recommended for certain other groups of children, including in areas where vaccination programs target older children. See *MMWR* 2006;55 [No. RR-7]:1–23.

7. Hepatitis B vaccine (HepB). *(Minimum age: birth)*
- Administer the 3-dose series to those who were not previously vaccinated.
- Post vaccination testing is recommended for HIV-infected persons. Testing should be performed 1–2 months after administration of the last dose of the vaccine series using a method that allows determination of a protective level of anti-HBs (≥10mIU/mL). Persons found to have anti-HBs levels of <10 mIU/mL after the primary series should be revaccinated. Administration of 3 doses on an appropriate schedule followed by anti-HBs testing 1–2 months after the 3rd dose is usually more practical than serologic testing after one or more doses of vaccine. Modified dosing regimens, including a doubling of the standard antigen dose might increase response rates. However, data on response to these alternative vaccination schedules are limited.
- In HIV infected persons, the need for booster doses has not been determined. Annual antiHBs testing and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in persons with ongoing risk of exposure. See *MMWR* 2005:54 [No. RR-16]:1–23.

8. Inactivated poliovirus vaccine (IPV). *(Minimum age: 6 weeks)*
- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age ≥4 years.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

9. Measles, mumps, and rubella vaccine (MMR). *(Minimum age: 12 months)*
- If not previously vaccinated and eligible, administer 2 doses of MMR vaccine during any visit, with ≥4 weeks between the doses.
- MMR vaccine is recommended for all asymptomatic HIV-infected children and adolescents who are not severely immunosuppressed (CD4+ age specific T-lymphocyte percentages <15% or T-lymphocyte count ≥200 cells/μL) and who lack evidence of measles immunity.
- MMR vaccine for symptomatic HIV-infected children and adolescents should be considered if they a) do not have evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages ≥15% or T-lymphocyte count ≥200 cells/μL) and b) lack evidence of measles immunity.
- MMRV vaccine has not been studied in HIV infected children and should not be substituted for MMR vaccine.
- MMR and other measles-containing vaccines are not recommended for HIV-infected children with evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages <15% or T-lymphocyte count <200 cells/μL). See *MMWR* 1998;47 [No. RR-8]:1-57, Special Considerations for Vaccination—Persons Infected with Human Immunodeficiency Virus [HIV]) (Table 2).

10. Varicella vaccine. *(Minimum age: 12 months)*
- Limited data are available on safety and immunogenicity of varicella vaccine in HIV infected children 1–8 years in CDC immunological categories 1 and 2, CD4+ age specific T-lymphocyte percentages ≥15%, and clinical categories N, A and B. Single antigen varicella vaccine should be considered for HIV-infected children 7–8 years without evidence of immunity with CD4+ age specific T-lymphocyte percentages ≥15% or T-lymphocyte count ≥200 cells/μL. Eligible children should receive 2 doses 3 months apart.
- Data on use of varicella vaccine in HIV-infected children >8 years and adolescents is lacking. However, on the basis of expert opinion, the safety of varicella vaccine in HIV-infected persons aged >8 years with similar levels of immune function (CD4+ age specific T-lymphocyte percentages ≥15% or T-lymphocyte count ≥200 cells/μL) is likely to be similar to that of children aged <8 years. Immunogenicity might be lower in HIV-infected adolescents (and adults). However, weighing the risk for severe disease from wild VZV and potential benefit of vaccination, vaccination (2 doses administered 3 months apart) for persons 9 to 18 years without evidence of immunity may be considered.
- MMRV vaccine has not been studied in HIV infected children and should not be substituted for single antigen varicella vaccine.
- Varicella vaccine is not recommended for HIV-infected children or adolescents with evidence of severe immunosuppression (CD4+ age specific T-lymphocyte percentages <15% or T-lymphocyte count <200 cells/μL).
- For evidence of immunity guidance and other details, see *MMWR* 2007;56 [No.RR-4]:1–40.

11. Hib vaccine. *(Minimum age: 6 weeks)*
Hib conjugate vaccines are available in single or combined antigen preparations. Hib vaccine is recommended routinely for all children through age 59 months. Clinicians and other health-care providers might consider use of Hib vaccine among persons >59 months with HIV infection who did not receive the vaccine as an infant or in childhood. See *MMWR* 2006:55 [No. RR-15]:1–48.

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