



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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### Panel's Recommendations

- Status of vaccination should be reviewed at every clinical encounter and indicated vaccinations provided, according to the established recommendations for immunization of HIV-infected children **(AIII)**.
- Routine use of antibiotics solely for primary prevention of serious bacterial infections is not recommended **(BIII)**. Discontinuation of antibiotic prophylaxis is recommended for HIV-infected children receiving antibiotics for the purpose of primary or secondary prophylaxis of serious bacterial infections once they have achieved sustained ( $\geq 3$  months) immune reconstitution: (CD4 T lymphocyte [CD4] cell percentage  $\geq 25\%$  if  $< 6$  years old; CD4 percentage  $\geq 20\%$  and CD4 count  $> 350$  cells/mm<sup>3</sup> if  $\geq 6$  years old) **(BII)**.
- Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (IgG  $< 400$  mg/dL) **(AI)**.
- HIV-infected children whose immune systems are not seriously compromised (CDC Immunologic Category I) and who are not neutropenic can be expected to respond the same as HIV-uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms **(AIII)**.
- Severely immunocompromised HIV-infected children with invasive or recurrent bacterial infections require expanded empiric antimicrobial treatment covering a broad range of resistant organisms **(AIII)**.
- Initial empiric therapy for HIV-infected children with suspected intravascular catheter sepsis should target both gram-positive and enteric gram-negative organisms, with combinations that have activity against *Pseudomonas* spp. and methicillin-resistant *Staphylococcus aureus* (MRSA) **(AIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

### Panel's Recommendations

- Uncomplicated oropharyngeal candidiasis (OPC) infection can be effectively treated with topical therapy using clotrimazole troches or nystatin suspension **(AII)**.
- Oral fluconazole is recommended for moderate or severe OPC disease **(AI\*)**.
- For fluconazole-refractory OPC, itraconazole oral solution is recommended, although it is less well tolerated than fluconazole **(AI)**.
- If OPC initially is treated topically, failure or relapse should be treated with oral fluconazole or itraconazole oral solution **(AI\*)**.
- Systemic therapy is essential for esophageal disease **(AI\*)**.
- Oral or intravenous fluconazole, amphotericin B, or an echinocandin (caspofungin, micafungin, anidulafungin), administered for 14 to 21 days, is highly effective for treatment of Candida esophagitis **(AI\*)**.
- For fluconazole-refractory esophageal disease, oral therapy can include itraconazole solution or voriconazole **(AIII)**.
- Central venous catheters should always be removed when feasible in HIV-infected children with candidemia **(AII)**.
- In severely ill children with candidemia, an echinocandin is recommended. In less severely ill children who have not had previous azole therapy, fluconazole is an alternative therapy **(AI\*)**.
- For patients infected with *Candida glabrata* or *Candida krusei*, an echinocandin is recommended **(AII\*)**.
- For patients infected with *Candida parapsilosis*, fluconazole or amphotericin B is recommended **(AII\*)**.
- Alternatively, an initial course of amphotericin B therapy can be administered for invasive candidiasis and then carefully followed by completion of a course of fluconazole therapy **(BIII)**.
- Data are insufficient to support routine use of combination antifungal therapy in children with invasive candidiasis **(BIII)**.
- The potential for drug interactions, particularly with antiretroviral drugs such as protease inhibitors, should be carefully evaluated before initiation of antifungal therapy **(AIII)**.
- Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate) or are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs **(BII)**.
- Children with candidemia should be treated for at least 14 days after documented clearance of Candida from the last positive blood culture and resolution of neutropenia and of clinical signs and symptoms of candidemia **(AII\*)**.

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## Coccidioidomycosis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended (**BIII**).
- Diffuse pulmonary or disseminated infection (not involving the central nervous system) should be treated initially with amphotericin B (**AII\***). After completion of amphotericin B, treatment with fluconazole or itraconazole should begin (**BIII**). Alternatively, some experts initiate therapy with amphotericin B combined with a triazole, such as fluconazole, in patients with disseminated disease and continue the triazole after amphotericin B is stopped (**BIII**).
- There is no evidence that lipid preparations of amphotericin are more effective than amphotericin B deoxycholate for the treatment of coccidioidomycosis. Lipid preparations are often preferred because they are better tolerated and associated with less nephrotoxicity than amphotericin B deoxycholate (**AII\***).
- For patients with mild disease (e.g., focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate (**BII\***).
- Itraconazole is preferred for treatment of skeletal infections (**AII\***).
- Because absorption of itraconazole varies from patient to patient, serum concentrations should be measured to ensure effective, non-toxic levels of drug, monitor drug levels following changes in dosage, and assess compliance (**BIII**).
- Amphotericin B preparations are not the drugs of choice for treating coccidioidal meningitis; fluconazole is the preferred drug for treating coccidioidal meningitis (**AII\***).
- Lifelong antifungal suppression (secondary prophylaxis) with either fluconazole or itraconazole is recommended for treating HIV-infected children after disseminated, diffuse pulmonary, and/or meningeal coccidioidomycosis (**AII\***), even if immune reconstitution is achieved with combination antiretroviral therapy (cART). Lifelong secondary prophylaxis should be considered for children with mild disease and CD4 T lymphocyte cell count  $<250$  cells/mm<sup>3</sup> or  $<15\%$ , even if immune reconstitution is achieved with cART (**BIII**).

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## Panel's Recommendations

- Routine use of antifungal medications is not recommended for primary prophylaxis of cryptococcal infections in children **(BIII)**.
- Combination therapy with amphotericin B deoxycholate (or liposomal amphotericin B) and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for central nervous system disease **(AI\*)**. Amphotericin B lipid complex is another alternative to amphotericin B deoxycholate **(BII\*)**.
- Liposomal amphotericin B is preferred over amphotericin B deoxycholate for patients with or at risk of renal insufficiency **(AI\*)**; amphotericin B lipid complex is an alternative **(BII\*)**.
- In patients who cannot tolerate flucytosine or if flucytosine is unavailable, amphotericin B deoxycholate (or liposomal amphotericin B or amphotericin B lipid complex) with or without high-dose fluconazole can be used for initial therapy **(BI\*)**. Fluconazole plus flucytosine is superior to fluconazole alone and an option in patients who cannot tolerate any form of amphotericin **(BII\*)**.
- Echinocandins are not active against cryptococcal infections and should not be used **(AIII)**.
- After a minimum of 2 weeks of induction therapy, if there is clinical improvement and a negative cerebrospinal fluid culture after repeat lumbar puncture, amphotericin B and flucytosine can be discontinued and consolidation therapy with fluconazole administered for a minimum of 8 weeks **(AI\*)**; itraconazole is a less preferable alternative to fluconazole **(BI\*)**.
- Secondary prophylaxis with fluconazole **(AI\*)** or itraconazole (less preferable) **(BI\*)** is recommended for a minimum of 1 year.
- Discontinuing secondary prophylaxis (after receiving secondary prophylaxis for  $\geq 1$  year) can be considered for asymptomatic children aged  $\geq 6$  years with CD4 counts  $\geq 100$  cells/mm<sup>3</sup> and an undetectable viral load on  $\geq 3$  months of combination antiretroviral therapy **(CIII)**. Secondary prophylaxis should be reinitiated if the CD4 count decreases to  $< 100$  cells/mm<sup>3</sup> **(AIII)**. Most experts would not discontinue secondary prophylaxis for patients younger than age 6 years **(CIII)**.
- 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)**. Those with mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy **(AIII)**.
- In antiretroviral-naïve patients newly diagnosed with cryptococcal meningitis or disseminated disease, delay in initiation of potent antiretroviral therapy may be prudent until the end of the first 2 weeks of induction therapy **(CIII)**.

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## Cryptosporidiosis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Reduce risk of *Cryptosporidium* infection by avoiding drinking water from public swimming pools and other bodies of recreational water (AIII), touching farm animals (BIII), and having contact with known *Cryptosporidium*-infected individuals (AIII).
- Combination antiretroviral therapy (cART) to prevent or reverse severe immune deficiency is the primary modality for preventing chronic *Cryptosporidium* infection in HIV-infected children (AII\*).
- Effective cART is the primary initial treatment for *Cryptosporidium* infections in HIV-infected children and adults (AII\*).
- Nitazoxanide can be considered in immunocompromised HIV-infected children in conjunction with cART for treatment of *Cryptosporidium* infection (BII\*).
- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (AIII).

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## Panel's Recommendations

- Cytomegalovirus (CMV) antibody testing is recommended at age 1 year and then annually for CMV-seronegative, HIV-infected infants and children who are immunosuppressed (i.e., CD4 T-lymphocyte (CD4) cell count <100 cells/mm<sup>3</sup> or CD4 percentage <10%) (**BII**).
- HIV-infected children aged <5 years who are CMV-infected and severely immunosuppressed (i.e., CD4 cell count <50 cells/mm<sup>3</sup> or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months (**AIII**).
- CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 cell count >100 cells/mm<sup>3</sup> in children aged ≥6 years, or CD4 percentage >10% in children <6 years (**BII**). Prophylaxis with valganciclovir can be considered for HIV-infected children aged ≥6 years who are CMV-seropositive and have CD4 cell counts <50 cells/mm<sup>3</sup> and for HIV-infected children aged <6 years who are CMV-seropositive and have a CD4 percentage <5% (**CIII**). Cessation of primary prophylaxis can be considered when the CD4 cell count is >100 cells/mm<sup>3</sup> for children ≥6 years of age, or >10% in children <6 years (**CIII**).
- Intravenous (IV) ganciclovir therapy (6 mg/kg/dose administered every 12 hours) for 6 weeks can be considered for HIV-exposed or HIV-infected infants who have symptomatic congenital CMV disease involving the central nervous system (CNS) (**BI**).
- For HIV-infected infants and children, IV ganciclovir is the drug of choice for initial treatment for acquired CMV disease, including retinitis and other end-organ disseminated CMV disease (e.g., colitis, esophagitis, CNS disease) (**AI\***). Oral valganciclovir has not been evaluated in HIV-infected children with CMV retinitis, but is an option primarily for older children who weigh enough to receive the adult dose and formulation of valganciclovir (**CIII**). Transition from IV ganciclovir to valganciclovir oral solution can be considered for younger patients who improve on IV therapy (**CIII**).
- Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children (**AI\***).
- Combination therapy with ganciclovir and foscarnet delays progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease (**BII**).
- Combination treatment with IV ganciclovir and foscarnet may be preferable as initial therapy to stabilize CMV neurologic disease and maximize response (**BII\***).
- Many experts would initially treat early first relapse of retinitis with reinduction using the same drug, followed by reinstatement of maintenance therapy (**AI\***). If drug resistance is suspected, change to an alternative drug is reasonable (**AIII**). Combination IV ganciclovir and foscarnet can be considered.
- After induction therapy, secondary prophylaxis (chronic maintenance therapy) is given for most forms of CMV disease until immune reconstitution or, in absence of immune reconstitution, for the remainder of a patient's life (**AI\***). Regimens recommended for chronic suppression include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and parenteral cidofovir (**AI\***).
- Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if relapses occur (**BII\***). A role for maintenance therapy for CMV pneumonitis has not been established (**CIII**).
- Discontinuing secondary prophylaxis may be considered for children who are receiving ART and have a sustained (such as >6 months) increase in CD4 cell count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 cell count to >100 cells/mm<sup>3</sup> for children aged ≥6 years (**CIII**).
- All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy has been discontinued should continue to undergo regular ophthalmologic monitoring at 3- to 6-month intervals for early detection of CMV relapse and for immune reconstitution uveitis (**AI\***).
- Secondary prophylaxis should be reinstated in HIV-infected children in whom it was discontinued because of immune reconstitution when the CD4 percentage decreases to <15% in those aged <6 years and when the CD4 cell count decreases to <100 cells/mm<sup>3</sup> in those aged ≥6 years (**BIII**).

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## Giardiasis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Giardiasis can be prevented by practicing good hygiene, avoiding drinking or swimming in water that may be contaminated, and not eating food that may be contaminated (**AIII**).
- Antiretroviral treatment of HIV-infected children to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric giardiasis (**AII\***).
- Combination antiretroviral therapy should be part of primary initial treatment for giardiasis in HIV-infected children (**AII\***).
- Dehydration and electrolyte abnormalities should be corrected (**AIII**).
- Patients with chronic diarrhea should be monitored for malabsorption leading to malnutrition (**AIII**).
- Tinidazole (**AII**) and nitazoxanide (**AI**) are preferred and metronidazole (**AI**) is the alternative recommended treatment for giardiasis in children.

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## Panel's Recommendations

- All pregnant women should be tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk of hepatitis B virus (HBV) infection (e.g., injection-drug users, women with intercurrent sexually transmitted diseases, women with multiple sex partners) **(BIII)**.
- All infants born to HBsAg-positive women, including HIV-co-infected women, should receive hepatitis B vaccine and hepatitis B immune globulin within 12 hours after birth, a second dose of hepatitis B vaccine at age 1 to 2 months, and a third dose at age 6 months **(AI)**.
- HIV-infected infants, children, and adolescents should be tested for HBsAg as soon as possible after HIV diagnosis **(AII)**.
- HIV-infected infants, children, and adolescents should be tested for quantitative anti-HBs and HBsAg 1 to 2 months after completing the vaccination series. If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, they should be revaccinated with a second, 3-dose series of HBV vaccine followed in 1 to 2 months by repeat testing for anti-HBs **(AIII)**.
- Antiviral therapy is not warranted in children without necroinflammatory liver disease **(BIII)**. Treatment is not recommended for children with immunotolerant chronic HBV infection (i.e. HBeAg positive, normal serum transaminase levels despite detectable HBV DNA) or inactive carriers (i.e. HBeAg negative, normal serum transaminase levels despite detectable HBV DNA) **(BII)**.
- Indications for treatment of chronic HBV infection in HIV-co-infected children are the same as in HBV-infected and HIV-uninfected children:
  - Evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>10,000–100,000 international units/ml for >6 months) and persistent elevation of serum transaminase levels (at least twice the upper limit of normal for >6 months), or
  - Evidence of chronic hepatitis on liver biopsy **(BII)**.
- Standard interferon-alfa (IFN- $\alpha$ ), IFN-2a or IFN-2b, is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged  $\geq 2$  years to <12 years who warrant treatment **(AI)**. IFN- $\alpha$  therapy or oral antiviral therapy with adefovir or tenofovir is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged  $\geq 12$  years **(AI)**. IFN- $\alpha$  therapy in combination with oral antiviral therapy cannot be recommended for pediatric HBV infection in HIV-uninfected children until more data are available **(BII)**.
- In HIV/HBV coinfecting children who do not require combination antiretroviral therapy (cART) for their HIV infection, IFN- $\alpha$  therapy is the preferred agent to treat chronic hepatitis B **(BIII)**, whereas adefovir can be considered in children age 12 years or older **(BIII)**.
- Treatment options for HIV/HBV co-infected children who meet criteria for HBV therapy and who are already receiving lamivudine- or emtricitabine-containing, HIV-suppressive cART include standard IFN- $\alpha$  therapy **(BIII)**, or adefovir if the child can receive adult dosing **(BIII)**, or use of tenofovir disoproxil fumarate (tenofovir) (with continued lamivudine or emtricitabine) in the cART regimen in children aged  $\geq 2$  years **(BIII)**.
- HIV/HBV-coinfecting children should not be given lamivudine or emtricitabine for treatment of chronic HBV unless accompanied by additional anti-HIV drugs in a cART regimen **(CIII)**.
- For HIV/HBV-coinfecting children who require treatment of both infections, a cART regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**.
- For HIV/HBV-coinfecting children aged  $\geq 2$  years who require treatment for HIV but not HBV infection or treatment for both infections, a cART regimen that includes tenofovir and an anti-HBV nucleoside (either lamivudine or emtricitabine) can be considered **(BIII)**.
- The dose of lamivudine required to treat HIV infection is higher than that used to treat pediatric chronic hepatitis B infection; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfecting children to avoid development of lamivudine-resistant HIV **(AIII)**.
- Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic hepatitis B and not additive **(BIII)**.
- For hepatitis B e antigen (HBeAg)-positive patients who are HIV-uninfected, treatment with anti-HBV drugs should be continued until HBeAg seroconversion has been achieved and >6 months of additional treatment has been completed after the appearance of anti-HBeAg **(BI\*)**. However, treatment with lamivudine or other anti-HBV drugs with anti-HIV activity should be continued indefinitely in children with HIV/HBV co-infection, even if HBeAg seroconversion occurs **(CIII)**.
- If discontinuation of therapy for chronic HBV results in hepatic flare, therapy for chronic HBV infection should be reinstated **(BIII)**.

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## Hepatitis C Virus (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Testing for hepatitis C virus (HCV) infection should be performed on any child whose mother is known to have the infection **(AIII)**. All HIV-infected adults and adolescents should be tested for HCV infection **(AII)**.
- Recommendations for route of delivery and infant feeding for HIV/HCV-coinfected women and their infants are the same as those for HIV-monoinfected women and their infants **(AII)**.
- Diagnostic evaluation for HCV infection in the first 18 months of life after HCV exposure: 2 negative HCV RNA tests at or after age 2 months, including one at or after age 12 months, definitively excludes HCV infection **(BIII)**. Two positive HCV RNA results before age 18 months are required for definitive diagnosis of HCV infection **(BIII)**.
- Diagnosis of HCV infection in the child older than age 18 months: Screen with anti-HCV antibody test and confirm active viral infection with HCV RNA polymerase chain reaction testing **(AIII)**.
- Adolescents should be counseled to avoid injection drug use; if using drugs, they need HCV (and HIV and HBV testing), and appropriate referral and therapy, including drug treatment. Other exposures, such as through unprotected sex, (commercial) tattooing and body-piercing, represent a much lower risk of transmission but should also be avoided **(BIII)**.
- All children (regardless of HIV and HCV infection status) should receive standard vaccination with hepatitis A and B vaccines **(AIII)**.
- Treatment of children aged <3 years who have HCV infection usually is not recommended **(BIII)**.
- Treatment should be considered for all HIV/HCV-coinfected children aged ≥3 years who have no contraindications to treatment **(BIII)**.
- A liver biopsy to stage disease is recommended before deciding whether to initiate therapy for chronic HCV genotype 1 infection **(BIII)**. However, some specialists would treat children infected with HCV genotypes 2 or 3 without first obtaining a liver biopsy **(BIII)**.
- Treatment of HCV-infected children, regardless of HIV status, should include interferon alfa (IFN-α) plus ribavirin combination therapy **(AI)**. Duration of treatment for HIV/HCV-coinfected children should be 48 weeks, regardless of HCV genotype **(BIII)**.
- Ribavirin and didanosine should not be used together **(AIII)**.
- When possible, ribavirin and zidovudine should not be administered simultaneously because both are associated with anemia **(BII\*)**.
- IFN-α therapy is contraindicated for children with decompensated liver disease, substantial cytopenias, renal failure, severe cardiac or neuropsychiatric disorders, and non-HCV-related autoimmune disease **(AII\*)**.
- Use of erythropoietin can be used to manage clinically significant anemia during HCV treatment **(AIII)**.

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## Herpes Simplex Virus Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- HIV-infected patients should use male latex condoms consistently and correctly during sexual intercourse to reduce the risk of exposure to herpes simplex virus (HSV) and other sexually transmitted pathogens (**AI\***). They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident (**AIII**).
- Although use of acyclovir or valacyclovir, beginning at 36 weeks of pregnancy to reduce the need for cesarean delivery, is recommended in HIV-uninfected women with recurrent genital herpes, data are insufficient to make a specific recommendation for HIV and HSV coinfecting women (**BIII**).
- For pregnant women who have active genital HSV lesions at the onset of labor, delivery by elective cesarean delivery, preferably before rupture of membranes, is recommended (**BII\***).
- Acyclovir is the drug of choice for treatment of local and disseminated HSV in infants and children, regardless of HIV-infection status (**AI**).
- Neonatal HSV disease should be treated with high-dose intravenous (IV) acyclovir (20 mg/kg body weight), administered for 21 days for central nervous system (CNS) and disseminated disease and for 14 days for disease of the skin, eyes, and mouth (**AI**). IV acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat cerebrospinal fluid HSV DNA polymerase chain reaction assay is negative near the end of treatment (**BIII**). Oral acyclovir prophylaxis for 6 months after treatment of neonatal disease involving the CNS or skin, eyes, and mouth can prevent cutaneous recurrences and may be associated with superior neurodevelopmental outcome in those with CNS disease (**AI**).
- Beyond the neonatal period, HSV encephalitis should be treated with IV acyclovir for 21 days (**AIII**).
- First-episode orolabial or genital lesions in HIV-infected children or adolescents can be treated with oral acyclovir for 7 to 10 days (**AI**). Children or adolescents with severe immunosuppression and moderate-to-severe mucocutaneous HSV lesions should be treated initially with IV acyclovir and may require longer therapy (**AI\***).
- Recurrent mucocutaneous lesions, if treated, are generally treated with oral acyclovir for 5 days (**AI\***).
- Alternatives to oral acyclovir in adolescents and adults include valacyclovir and famciclovir (**AI\***).
- Patients with acute retinal necrosis should receive combination antiretroviral therapy and high-dose IV acyclovir for 10 to 14 days, followed by prolonged (i.e., 4–6 weeks) oral therapy, such as valacyclovir or acyclovir (**AIII**).
- HSV keratoconjunctivitis is usually treated with topical trifluridine or oral acyclovir alone, although many experts recommend the combination (**AII\***).
- The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI\***).
- Children or adolescents who have frequent or severe orolabial or genital recurrences can be given daily suppressive therapy with oral acyclovir (**AI\***). Valacyclovir and famciclovir also are options for adolescents (**AI\***).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Panel's Recommendations

- Routine use of antifungal medications for primary prophylaxis of histoplasmosis in children is not recommended (**BIII**).
- Amphotericin B is preferred for initial treatment of moderately severe to severe infections (**AI\***).
- Itraconazole is the azole preferred for treatment of histoplasmosis (**AIII**).
- In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for 1 year thereafter to identify relapse (**AIII**).
- For severe or moderately severe acute primary pulmonary histoplasmosis, amphotericin B should be administered for at least 1 to 2 weeks (and clinical improvement) (**AIII**). After treatment with amphotericin, patients with intact immunity should receive itraconazole for at least 12 weeks (**AIII**). Adults with CD4 T lymphocyte (CD4) cell counts  $<150$  cells/mm<sup>3</sup> and HIV-infected children with severe immunosuppression should receive itraconazole consolidation therapy for at least 12 months (**AIII**).
- The preferred treatment for severe or moderately severe progressive disseminated histoplasmosis is initial (induction) therapy with amphotericin B for  $\geq 2$  weeks (and favorable clinical response), followed by consolidation therapy with itraconazole for at least 12 months (**AI\***).
- Itraconazole monotherapy for 12 months is recommended for HIV-infected children with mild to moderate progressive disseminated histoplasmosis (**AII\***).
- Liposomal amphotericin B for 4 to 6 weeks is the preferred initial treatment in the presence of focal brain lesions (**BIII\***). Thereafter, children should receive itraconazole consolidation therapy for at least 12 months and until cerebrospinal fluid abnormalities, including histoplasma antigen, have resolved (**AII\***).
- In the event of immune reconstitution inflammatory syndrome, antiretroviral therapy should be continued along with antifungal therapy (**AIII**).
- Longer-term suppressive therapy (secondary prophylaxis) with itraconazole may be required in HIV-infected children who are severely immunosuppressed (meaning CD4 percentage  $<15\%$  at any age or CD4 count  $<150$  cells/mm<sup>3</sup> in children aged  $\geq 6$  years) and patients who experience relapse despite receipt of appropriate therapy (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Human Herpesvirus 8 Disease (Last updated December 15, 2016; last reviewed December 15, 2016)

### Panel's Recommendations

**I. Is there an indication for serologic testing for human herpesvirus 8 (HHV-8) in asymptomatic HIV-infected children (compared with not testing) to guide clinical management?**

Antibody (or DNA testing) for HHV-8 is insufficiently sensitive/specific to predict risk of Kaposi sarcoma. Therefore, routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended (**strong, very low**).

**II. Among HIV-infected children, does initiation of antiretroviral therapy (ART) (as compared with non-initiation) reduce the risk of Kaposi sarcoma?**

Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated Kaposi sarcoma (**strong, low**).

**III. For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of Kaposi sarcoma?**

Data are insufficient and conflicting upon which to base a recommendation for a particular ART regimen for prevention of Kaposi sarcoma (**weak, low**).

**IV. Among HIV-infected children with active Kaposi sarcoma, is treatment with ART (as compared with no ART) associated with higher rates of remission and/or decreased mortality?**

Treatment with ART is associated with increased survival among HIV-infected children with active Kaposi sarcoma. Effective suppression of HIV replication with ART is recommended for all patients with evidence of active Kaposi sarcoma and other HHV-8-associated malignant lymphoproliferative disorders (**strong, very low**).

**V. Among HIV-infected children with active Kaposi sarcoma, is treatment with chemotherapy in addition to ART (as compared with ART alone) associated with higher rates of remission and/or decreased mortality?**

Systemic chemotherapy, in addition to ART, is associated with higher rates of remission and decreased mortality and is recommended for disseminated or visceral Kaposi sarcoma (stage T1 disease) and for primary effusion lymphoma (**strong, low**). For localized Kaposi sarcoma (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear.

**VI. Among HIV-infected children treated with ART who develop immune reconstitution inflammatory syndrome (IRIS), is chemotherapy in addition to continuation of ART (compared with no chemotherapy) associated with higher rates of remission and/or decreased mortality?**

For patients with Kaposi-sarcoma-associated IRIS, chemotherapy along with continuation of ART is recommended (**strong, low**).

**VII. Among HIV-infected children who achieve remission from Kaposi sarcoma, what therapies are recommended to lower the risk of recurrence?**

Effective suppression of HIV replication with ART in HIV-infected patients with Kaposi sarcoma may prevent Kaposi sarcoma progression or occurrence of new lesions and may decrease risk of recurrence after remission. Life-long ART is recommended for all individuals with evidence of active or treated Kaposi sarcoma or other HHV-8-associated malignant lymphoproliferative disorders (**strong, low**).

### Rating System

*Strength of Recommendation:* Strong; Weak

*Quality of Evidence:* High; Moderate; Low; or Very Low

# Human Papillomavirus (HPV) (Last updated November 6, 2013; last reviewed November 6, 2013)

## Panel's Recommendations

- HIV-infected individuals should use latex condoms during every act of sexual intercourse to reduce the risk of exposure to sexually transmitted pathogens, including human papillomavirus (HPV) **(AII)**.
- Ideally, HPV vaccine should be administered before an individual becomes sexually active **(AIII)**.
- HPV vaccination is recommended in HIV-infected females and males aged 11 to 12 **(AIII)** and 13 to 26 **(BIII)** years. HPV vaccination also can be administered to HIV-infected males and females aged 9 to 10 years. The bivalent and quadrivalent vaccines are approved for females and the quadrivalent vaccine is approved for males.
- Sexually active female adolescents who are HIV-infected should have routine cervical cancer screening whether or not they have been vaccinated **(AIII)**.
- HIV-infected female adolescents who have initiated sexual intercourse should have cervical screening cytology (liquid-based or Pap smear) obtained twice at 6-month intervals during the first year after diagnosis of HIV infection, and if the results are normal, annually thereafter **(AII)**. A Pap smear should be performed within 1 year of onset of sexual activity, regardless of age or method of HIV transmission **(BIII)**.
- If the results of the Pap smear are abnormal, in general, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by the American Society for Colposcopy and Cervical Pathology (<http://www.asccp.org/ConsensusGuidelines/tabid/7436/Default.aspx>).
- HIV-infected adolescent females should be referred for colposcopy if they have any of the following: squamous intraepithelial lesion (SIL), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells—cannot exclude a high grade intraepithelial lesion (ASC-H). For HIV-infected adolescent females with atypical squamous cells of undetermined significance (ASC-US), either immediate referral to colposcopy or repeat cytology in 6-12 months is recommended. If ASC-US or greater is found on repeat cytology, referral to colposcopy is warranted **(BIII)**. Use of HPV testing is not recommended for screening or for triage of HIV-infected women with abnormal cytology results or follow-up after treatment **(BIII)**.
- Because of the high rate of recurrence after treatment, conservative management of cervical intraepithelial neoplasia-1 (CIN1) and CIN2 with observation is the preferred method for HIV-infected adolescent females **(BIII)**.
- Because risk of recurrence of CIN and cervical cancer after conventional therapy is increased in HIV-infected females, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)**.
- Genital warts should be treated per the 2010 Centers for Disease Control and Prevention STD treatment guidelines (located at <http://www.cdc.gov/std/treatment/2010/>)

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents



## Influenza (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- The approach to evaluation and treatment of HIV-infected children on stable combination antiretroviral therapy with suspected or confirmed influenza should be similar to that of HIV-uninfected children (**AIII**). HIV-infected children with evidence of moderate-to-severe immunosuppression by CD4-defined or clinical disease-defined categories may be at increased risk of influenza-related complications and should be monitored closely until illness resolution (**BII**).
- Prevention of influenza in HIV-infected children aged 6 months and older should include annual administration of trivalent inactivated influenza vaccine, according to Advisory Committee on Immunization Practices recommendations (see annual updated recommendations at <http://www.cdc.gov/vaccines/pubs/acip-list.htm>) (**AII**).
- Influenza-specific antiviral chemoprophylaxis should be considered for HIV-infected children based on level of immunosuppression and other preexisting co-morbidities, influenza vaccination status, and degree of exposure to suspected or confirmed influenza, according to CDC guidelines (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>) (**BII**).
- HIV-infected children with confirmed influenza should be considered for prompt antiviral therapy, according to CDC guidelines (see <http://www.cdc.gov/flu/antivirals/> and <http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf>) (**AII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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## Isosporiasis (Cystoisosporiasis) (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Antiretroviral treatment of HIV-infected children to reverse or prevent severe immunodeficiency may reduce the incidence or prevent recurrence of isosporiasis (**CIII**).
- Careful hand washing and thorough washing of fruits and vegetables are recommended to prevent exposure (**AIII**).
- Travelers to endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables, all of which can be contaminated (**BIII**).
- Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in HIV-infected children (**AI\***).
- In those with severe immunosuppression, treatment should be followed by secondary prophylaxis with TMP-SMX until severe immunosuppression resolves (**AII\***).
- As with all causes of diarrhea, supportive care, including replenishment of fluids and electrolytes, is essential (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents



### Panel's Recommendations

- Families traveling to malaria-endemic countries should receive pre-travel counseling, including information on insecticide-treated bed nets, N,N-Diethyl-meta-toluamide, and country-specific antimalarial prophylaxis **(AII)**.
- Trimethoprim-sulfamethoxazole is not recommended for antimalarial prophylaxis **(AIII)**.
- Treatment of malaria is based on disease severity, patient age, parasite species, pregnancy status, and local resistance patterns where the malaria infection was acquired **(AI)**.
- The choice of malaria therapy is not affected by HIV status but can be modified based on potential interactions between antiretroviral and antimalarial drugs **(AIII)**. Quinidine is not recommended for patients who are taking ritonavir **(AIII)** (ritonavir may be replaced if quinidine is needed for severe malaria) and should be administered with caution with atazanavir, darunavir and fosamprenavir **(AIII)**.
- The treatment options for uncomplicated chloroquine-susceptible *Plasmodium falciparum* malaria include chloroquine phosphate, atovaquone-proguanil, artemether-lumefantrine, and quinine sulfate plus either doxycycline, tetracycline (in children aged  $\geq 8$  years), or clindamycin. Mefloquine is considered an alternative regimen **(AIII)**.
- Chloroquine should not be used to treat malaria infections acquired in areas with chloroquine resistance **(AIII)**.
- Treatment of uncomplicated chloroquine-resistant malaria may include atovaquone-proguanil, quinine sulfate plus either doxycycline or tetracycline (specifically in children aged  $\geq 8$  years) or clindamycin or artemether-lumefantrine **(AIII)**.
- Treat for presumptive chloroquine-resistant *P. falciparum* malaria in symptomatic patients who have traveled to a region with chloroquine-resistant *P. falciparum* and for whom reliable identification of the malaria species is not possible or who are severely ill **(AIII)**.
- After initial treatment for *Plasmodium vivax* and *Plasmodium ovale* (same as for uncomplicated *P. falciparum*), primaquine is recommended for treatment of the dormant liver stage (hypnozoites) **(AIII)**.
- Glucose-6-phosphate dehydrogenase deficiency must be excluded before use of primaquine because of risk of severe hemolytic anemia **(AIII)**.
- Treatment of severe malaria includes both IV quinidine gluconate plus either doxycycline **OR** clindamycin **OR** tetracycline. Alternatives include artesunate IV (under Investigational New Drug protocol: Contact the Centers for Disease Control and Prevention Malaria Hotline at (770) 488-7788) followed by either doxycycline **OR** atovaquone-proguanil **OR** mefloquine **OR** clindamycin **(AIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

### Panel's Recommendations

#### I. In children with HIV infection, what are the best interventions (compared with no intervention) to treat microsporidiosis?

- Effective antiretroviral therapy (ART) is the primary initial treatment for microsporidiosis in HIV-infected children (**strong, very low**).
- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (**expert opinion**).
- Albendazole, in addition to ART, is also recommended for initial therapy of microsporidiosis caused by microsporidia other than *Enterocytozoon bieneusi* and *Vittaforma corneae* (**strong, low**).
- Systemic fumagillin (where available), in addition to ART, is recommended for microsporidiosis caused by *E. bieneusi* and *V. corneae* (**strong, moderate**).
- Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia (**strong, very low**).
- Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis due to microsporidia other than *E. bieneusi* and *V. corneae* (**expert opinion**).

#### II. In HIV-infected children who have been treated for microsporidiosis, when can treatment (secondary prophylaxis) be safely discontinued?

Clinicians may consider continuing treatment for microsporidiosis until improvement in severe immunosuppression is sustained (more than 6 months at Centers for Disease Control and Prevention immunologic category 1 or 2) and clinical signs and symptoms of infection are resolved (**weak, very low**).

#### Rating System:

*Strength of Recommendation:* Strong, weak

*Quality of Evidence:* High; Moderate; Low; or Very Low

# ***Mycobacterium avium* Complex Disease** (Last updated November 6, 2013; last reviewed November 6, 2013)

## **Panel's Recommendations**

- Routine screening of respiratory or gastrointestinal specimens for *Mycobacterium avium* complex (MAC) microorganisms is not recommended (**BIII**), but a blood culture for MAC should be obtained to rule out disseminated disease before initiating prophylaxis (**AIII**).
- Prophylaxis with either clarithromycin or azithromycin should be offered to HIV-infected children who have advanced immunosuppression (**AII**).
  - Children aged <1 year: <750 cells/mm<sup>3</sup>
  - Children aged 1 to <2 years: <500 cells/mm<sup>3</sup>
  - Children aged 2 to <6 years: <75 cells/mm<sup>3</sup>
  - Children aged ≥6 years: <50 cells/mm<sup>3</sup>

### Discontinuing Primary Prophylaxis:

- Primary prophylaxis can be discontinued in HIV-infected children aged ≥2 years receiving stable combination antiretroviral therapy (cART) for ≥6 months and experiencing sustained (>3 months) CD4 T lymphocyte (CD4) cell count recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults, >100 cells/mm<sup>3</sup> for children aged ≥6 years (**AI**); and >200 cells/mm<sup>3</sup> for children aged 2 to <6 years) (**BII\***).

### Treating Disease:

- Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (**BIII**). Combination therapy with a minimum of two drugs (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (**AI\***). 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 (**AI\***).
- Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial. Some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen, particularly in the absence of cART and in the presence of high mycobacterial counts (**CIII**); however, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy (**AIII**). Other experts recommend against using this third agent in children because of rifabutin's increased cytochrome P450 activity, which leads to increased clearance of other drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and the potential for increased toxicity associated with concomitant administration of drugs (**CIII**).
- Treatment failure is defined as 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 situation, 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 for this scenario include rifabutin, amikacin, and a quinolone.

### Secondary Prophylaxis:

- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (**AI\***). Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.
- Some experts recommend discontinuation of therapy in HIV-infected children who meet **all** of the following criteria:
  - Aged ≥2 years and have completed ≥12 months of treatment for MAC;
  - Remain asymptomatic for MAC;
  - Receiving stable cART (i.e., cART not requiring change for virologic or immunologic failure);
  - Have sustained (≥6 months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (i.e., as in adults, >100 cells/mm<sup>3</sup> for children aged ≥6 years (**AI\***) and >200 cells/mm<sup>3</sup> for children aged 2 to <6 years) (**CIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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# ***Mycobacterium tuberculosis*** (Last updated November 6, 2013; last reviewed November 6, 2013)

## **Panel's Recommendations**

### Detection of Latent TB Infection

- Diagnostic methods for latent tuberculosis (TB) infection (LTBI) include the tuberculin skin test (TST), administered by the Mantoux method with an Food and Drug Administration (FDA)-approved purified protein derivative, or FDA-approved interferon gamma release assays (IGRA) (QuantiFERON<sup>®</sup>-TB Gold In-Tube, and T SPOT<sup>®</sup>.TB); TST is preferred over IGRA in children aged <5 years (**BII**).
- TST and IGRA **should NOT** be used to rule out disease and cannot replace regular screening for TB exposure (**AII**). In high-TB-burden settings, screening for TB exposure and for signs or symptoms suggestive of TB disease is universally applicable and should occur at every health care visit (**AII**).

### Treatment for LTBI

- HIV-infected children should receive preventive therapy if they have a positive TST or IGRA result or if they are exposed to an individual with infectious TB (regardless of previous treatment for TB or the TST or IGRA result), after TB disease has been excluded (**AII**).
- The preferred preventive therapy regimen is isoniazid daily for 9 months (**AII**). If adherence with daily isoniazid cannot be ensured, then consider twice-weekly isoniazid by directly observed therapy (DOT) by a trained worker, not a family member (**BII**).
- With exposure to an isoniazid mono-resistant source case, preventive therapy consisting of daily rifampin for 6 months is recommended, with adjustment of combination antiretroviral therapy (cART) as required (**BII**).
- A 12-dose combination regimen of once-weekly isoniazid and rifapentine by DOT is as safe and effective as other regimens in preventing TB disease, and the completion rate is greater than for longer regimens. However, pediatric experience with this regimen is limited, and drug-drug interactions between rifapentine and other antiretroviral drugs have not been determined. This regimen is not recommended for children aged <2 years, nor for HIV-infected adults or children who are receiving cART or individuals who have LTBI with presumed isoniazid or rifampin resistance; the preferred regimen for children aged 2 to 11 years remains daily isoniazid for 9 months.

### Treatment of TB Disease

- In children diagnosed with TB, DOT must be started immediately (**AII**) and all cases of suspected and confirmed TB disease must be reported to the relevant health authorities.
- All children diagnosed with TB should be tested for HIV infection (**AIII**).
- In HIV-infected children, the recommended treatment for fully-drug-susceptible TB is a 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive phase, followed by a 7-month continuation phase using only isoniazid and rifampin (**AII**), with adjustment of cART as required. With good adherence and treatment response, thrice-weekly treatment under DOT during the continuation phase can be considered (**CII**).
- For children with extrapulmonary disease caused by drug susceptible TB involving the bones or joints, central nervous system (CNS), or disseminated/miliary disease, the recommended duration of treatment is 12 months (**AIII**).
- For TB meningitis (TBM), pending drug-susceptibility testing results, ethionamide can replace ethambutol (or an injectable aminoglycoside) as the fourth drug because of its superior cerebrospinal fluid penetration (**CII**).
- Children with suspected and confirmed multidrug resistant (MDR) TB (i.e., resistance to both isoniazid and rifampin) should be managed in consultation with an expert. In the United States, treatment of MDR-TB should be individualized based on drug susceptibility test (DST) results (in cases where DST results for the child are not available, then DST results for the source case should be used to guide initial choice of regimen) (**AII**).
- Treatment for TB must commence as soon as the diagnosis is established in HIV-infected children, both those who are already on cART and those not yet receiving cART; those not yet on cART should be evaluated for early cART initiation, preferably within 2 to 8 weeks of starting TB therapy (**AII**).
- Depending on age and previous cART exposure, an efavirenz-based regimen usually is preferable because such regimens are associated with better treatment outcomes (**AII**). Nevirapine with potential dose adjustment with concomitant rifampin administration can also be considered (**CIII**).
- If a protease inhibitor-based regimen is used, superboosting with ritonavir (using a ritonavir dose equal to the lopinavir dose) for the full duration of rifampin treatment (and 2 weeks after termination) is required (**AII**).
- Pyridoxine supplementation (1-2 mg/kg body weight/day, max 50 mg/day) is recommended for all HIV-infected children who are taking isoniazid (**AII**) or cycloserine (**AIII**).
- Adjunctive corticosteroids treatment (with ongoing treatment for TB) is indicated for children with TBM or pericardial effusion (**AII**). It can also be considered with severe immune reconstitution inflammatory syndrome, airway compression, or pleural effusion (**BII**).

### Panel's Recommendations, continued

- Liver chemistry tests should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (the same for cART initiation while receiving treatment for TB) **(BIII)**. Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving cART, or more frequently if clinically indicated **(BIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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# ***Pneumocystis jirovecii* Pneumonia** (Last updated November 6, 2013; last reviewed November 6, 2013)

## **Panel's Recommendations**

### Prevention of Primary Exposure

- Some experts recommend that consideration be given to not placing a patient with *Pneumocystis jirovecii* pneumonia (PCP) in a hospital room with another patient and not placing an at-risk immunocompromised patient in a room with a patient who has a respiratory tract infection (**BIII**).

### Chemoprophylaxis

- Chemoprophylaxis is highly effective in preventing PCP. Prophylaxis is recommended for all HIV-infected children aged  $\geq 6$  years who have CD4 T lymphocyte (CD4) cell counts  $< 200$  cells/mm<sup>3</sup> or CD4 percentage  $< 15\%$ , for children aged 1 to  $< 6$  years with CD4 counts  $< 500$  cells/mm<sup>3</sup> or CD4 percentage  $< 15\%$ , and for all HIV-infected infants aged  $< 12$  months regardless of CD4 count or percentage (**AII**).
- Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be HIV-uninfected or presumptively HIV-uninfected (**AIII**). HIV-infected infants should be administered prophylaxis until age 1 year, at which time they should be reassessed on the basis of the age-specific CD4 count or percentage thresholds mentioned above (**AII**).
- Trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole), administered either on 3 consecutive days/week or daily, is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum (**AI**).
- Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone (**AI**) or dapsone (**BI\***).
- Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and who are old enough to use nebulization with a Respigard II<sup>®</sup> nebulizer (Marquest; Englewood, CO) (**BI\***).
- Intravenous (IV) pentamidine is not recommended for prophylaxis unless no other options are available (**BII**).
- Discontinuation of PCP prophylaxis should be considered for HIV-infected children when, after receiving combination antiretroviral therapy for  $\geq 6$  months, CD4 percentage is  $\geq 15\%$  or CD4 count is  $\geq 200$  cells/mm<sup>3</sup> for patients aged  $\geq 6$  years (**BII**) and CD4 percentage is  $\geq 15\%$  or CD4 count is  $\geq 500$  cells/mm<sup>3</sup> for patients aged 1 to  $< 6$  years (**BII**) for  $> 3$  consecutive months. Thereafter, CD4 percentage and CD4 count should be reevaluated at least every 3 months and prophylaxis reinstated if the age-specific criteria for prophylaxis are reached (**BIII**).

### Treatment

- TMP-SMX, administered IV, is the recommended treatment for PCP (**AI**). As the acute pneumonitis subsides, children with mild-to-moderate disease who do not have malabsorption or diarrhea can be transitioned to oral treatment with the same total daily dose of TMP-SMX administered in 3 or 4 divided doses to complete a 21-day course (**AII**).
- IV pentamidine isethionate once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy (**AI\***).
- Atovaquone is an alternative for treatment of mild-to-moderately severe PCP (**BI\***).
- Dapsone/TMP is effective in treating mild-to-moderate PCP (**BI\***).
- Clindamycin/primaquine has been used to treat mild-to-moderate PCP; data in children are unavailable (**BIII**).
- A short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis (**AI\***).
- Patients who have experienced an episode of PCP should continue on PCP prophylaxis after completion of treatment until CD4 counts exceed the threshold for initiating prophylaxis (**AI**).
- Children 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 (**BI\***).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Progressive Multifocal Leukoencephalopathy (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- The main approach to treatment of Progressive Multifocal Leukoencephalopathy (PML) is treatment with an effective antiretroviral regimen that suppresses HIV viremia and preserves or restores CD4 T-lymphocyte (CD4) cell-defined immune function **(AII)**.
- Intrathecal cytosine arabinoside and cidofovir are not routinely recommended for treatment of PML **(BIII)**.
- Immunomodulatory approaches, such as interferon alfa, are not routinely recommended for treatment of PML **(BIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

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## Panel's Recommendations

### Congenital Syphilis

- Infants should be evaluated and treated per guidelines for congenital syphilis, given the following maternal factors:
  - Untreated or inadequately treated syphilis (including treatment with erythromycin or any other non-penicillin regimen)
  - Lack of documentation of having received treatment,
  - Receipt of treatment <30 days before delivery,
  - Treatment with penicillin but maternal nontreponemal antibody titer at delivery is fourfold higher than the pretreatment titer, or
  - Fourfold or greater increase in nontreponemal antibody titer suggesting relapse or reinfection **(AII)**.
- **Note:** For comprehensive discussion and recommendations, see [Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines, 2010](#).
- Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G for 10 days **(AII)**.
- If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous crystalline penicillin G should be increased per treatment guidelines **(AII)**.
- An alternative to aqueous crystalline penicillin G is procaine penicillin G for 10 days **(BII)**.
- All seroreactive infants (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (a nontreponemal test) every 2 to 3 months until the test becomes nonreactive or the titer has decreased fourfold **(AIII)**. Infants whose initial cerebrospinal fluid (CSF) evaluations are abnormal should undergo repeat lumbar puncture approximately every 6 months until the results are normal **(AII)**.
- After treatment of congenital syphilis, children with increasing or stable nontreponemal titers at ages 6 to 12 months should be evaluated (i.e., including a CSF examination) and treated with a 10-day course of parenteral penicillin **(AIII)**.
- Infants in whom the nontreponemal test is reactive at age 18 months should be fully evaluated or re-evaluated (physical, serological, CSF, radiographic exams) and treated or re-treated for congenital syphilis **(AIII)**.

### Sexually-Acquired Syphilis

#### *Early Syphilis*

- Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G for early-stage disease (i.e., primary, secondary, and early latent disease) **(AII)**.
- HIV-infected children and adolescents with early syphilis (i.e., primary, secondary, early latent) should receive a single dose of benzathine penicillin G. Those with primary and secondary syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy, and those with early latent syphilis should have clinical and serologic response monitored at 6, 12, 18, and 24 months after therapy **(AIII)**. (For comprehensive discussion and recommendations, see [the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010](#)).
- Re-treatment of patients with early-stage syphilis (i.e., primary, secondary, early latent) and evaluation for HIV infection is recommended for those who:
  - Do not experience at least a fourfold decrease in serum nontreponemal test titers 6 to 12 months after therapy,
  - Have a sustained fourfold increase in serum nontreponemal test titers after an initial reduction post-treatment, or
  - Have persistent or recurring clinical signs or symptoms of disease.
- Individuals whose titers do not decline should at a minimum receive additional clinical and serologic follow-up. If such additional follow-up cannot be ensured, re-treatment is recommended. Because occult central nervous system infection may be signaled by persistently elevated serum nontreponemal test titers, evaluation of CSF can be considered in the event of such persistently elevated titers **(BIII)**.
- If initial CSF examination demonstrates pleocytosis, repeat lumbar puncture should be conducted, and then every 6 months until the cell count is normal **(AIII)**.

#### *Late Latent Syphilis*

- For late latent disease, 3 doses of benzathine penicillin G should be administered over 3 weeks **(AIII)**.
- Patients with late-latent syphilis should have CSF examination if they have clinical signs or symptoms attributable to syphilis, a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (i.e., less than fourfold decline in nontreponemal test titer) within 12 to 24 months after therapy if initial titer was high (>1:32) **(BIII)**. CSF examination

## Panel's Recommendations, continued

should also be performed. Treatment for neurosyphilis should be initiated if CSF examination is positive for neurosyphilis.

- Benzathine penicillin G should be administered at 1-week intervals for 3 weeks to patients in whom CSF examination does not confirm the diagnosis of neurosyphilis (**AIII**).

### *Neurosyphilis*

- Neurosyphilis should be treated with aqueous penicillin G for 10 to 14 days (**AII**).
- If a patient has signs or symptoms consistent with neurosyphilis, and repeat CSF examination is consistent with CNS involvement and cannot be attributable to other ongoing illness, re-treatment for neurosyphilis is recommended (**AIII**);
- Re-treatment of neurosyphilis should be considered if the CSF white blood cell count has not decreased 6 months after completion of treatment or if the CSF white blood cell count or protein is not normal 2 years after treatment (**BIII**).

### For All Syphilis

- For penicillin-allergic patients or for a discussion of alternative therapies such as doxycycline, ceftriaxone, or azithromycin, please see pages 30, 34, and 38 of [the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010](#).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

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## Panel's Recommendations

### Preventing Exposure

- Ingestion of undercooked meats that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts should be avoided (**AIII**).

### Initiating Primary Prophylaxis

- *Toxoplasma*-seropositive children aged <6 years with CD4 T lymphocyte (CD4) cell percentage <15% and children aged ≥6 years with CD4 <100 cells/mm<sup>3</sup> should be administered prophylaxis against *Toxoplasma* encephalitis (TE) (**AIII**). The preferred agent for prophylaxis of TE is trimethoprim-sulfamethoxazole, one double-strength tablet daily for adolescents and adults (or weight-equivalent dosing for children) (**AI\***).
- Primary preventive therapy can be discontinued once a child responds to combination antiretroviral therapy (cART) with a sustained rise in CD4 percentage above 15% for children <6 years of age, and >200 cells/mm<sup>3</sup> for children aged ≥6 years (**BIII**).
- Most experts recommend treating pregnant women with acute toxoplasmosis in an attempt to prevent fetal infection (**BII**). For more extensive information on diagnosis, prevention, and treatment of pregnant women with toxoplasmosis, please see the [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#).
- Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary *Toxoplasma* infection during pregnancy, regardless of whether treatment was administered during pregnancy (**BIII**).
- The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (**AII**).
- The recommended duration of treatment of congenital toxoplasmosis in HIV-infected infants is 12 months (**AIII**).
- Therapy for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin (**AI\***).
- Corticosteroids are recommended for HIV-infected children with central nervous system toxoplasmosis when cerebrospinal fluid protein is highly elevated (i.e., >1,000 mg/dL) or who have focal lesions with substantial mass effect (**BIII**). Anticonvulsants should be administered only to children with TE who have a history of or current seizures (**AIII**).
- Complete blood count should be monitored weekly in patients taking daily pyrimethamine (**AIII**). Patients who have completed initial therapy for TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) unless cART results in immune reconstitution (**AI\***).
- The preferred regimen for suppressive therapy for TE is sulfadiazine plus pyrimethamine and leucovorin (**AI\***).

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## Varicella-Zoster Virus (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- HIV-infected children and adults who have no evidence of immunity to varicella should avoid exposure to people with varicella or zoster (**AIII**). Household contacts of HIV-infected patients should receive varicella vaccine if they lack evidence of immunity to avoid the possibility of transmitting wild-type varicella-zoster virus (VZV) to their HIV-infected contacts (**AIII**).
- HIV-infected children aged 1 through 8 years without evidence of varicella immunity and whose CD4 T lymphocyte (CD4) cell counts are  $\geq 15\%$  should be considered for 2 doses of varicella vaccine, the first dose administered as early as age 12 to 15 months (or as soon as possible after the first birthday) and the second dose 3 months later (**BII**). Older children with comparable levels of immune function (i.e., CD4 cell counts  $\geq 200$  cells/mm<sup>3</sup>) who lack varicella immunity may be considered for 2 doses of varicella vaccine administered 3 months apart (**BIII**).
- Combination measles-mumps-rubella-varicella vaccine should not be administered to HIV-infected children (**AIII**).
- HIV-infected children with low CD4 percentages ( $<15\%$ ) should not be vaccinated against varicella (**AIII**). Vaccination of such children can be safely undertaken after reconstitution of their immune systems (CD4 percentage  $\geq 15\%$ ) with combination antiretroviral therapy (cART) for at least 3 months (**AII**). Herpes zoster (HZ) vaccine should not be given to HIV-infected children (**AIII**).
- HIV-infected children and adolescents who:
  - 1) lack evidence of immunity to varicella, and
  - 2) have a non-transient exposure to a contact with varicella or herpes zostershould receive VZV immunoglobulin prophylaxis as soon as possible (ideally within 96 hours but potentially beneficial up to 10 days) after the close contact (**AII**). Many experts limit this recommendation to varicella- or zoster-exposed HIV-infected children who are considered to be severely immunocompromised (i.e., CDC Immunologic Category 3) especially if they have high HIV viral loads and would be classified in CDC Clinical Category C (**BIII**). When passive immunization is impossible, some experts recommend prophylaxis with acyclovir beginning 7 to 10 days after exposure, while others consider it prudent to wait until the first appearance of rash to start acyclovir therapy in VZV-susceptible and VZV-exposed, HIV-infected children (**CIII**).
- Acyclovir is the drug of choice for treating VZV infection in HIV-infected children (**AI**). Intravenous (IV) acyclovir is recommended for treating varicella in HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3) and those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions (**AIII**). Oral acyclovir should only be used to treat varicella in HIV-infected children who are in CDC Immunologic Category 1 or 2 and who have mild varicella disease (**BIII**).
- Acyclovir is the oral treatment of choice for zoster in HIV-infected children, given for 7 to 10 days, although longer durations of therapy should be considered if lesions are slow to resolve (**AII\***). Oral administration of acyclovir for HZ is considered safe for children with mild to moderate immune suppression (**AII**). Initial IV administration is recommended for HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3), extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ (**AII\***). It can also be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving (**AIII**), after which oral administration can be considered to complete the course of therapy—10 to 14 days in this situation (**AIII**).
- Recommended treatment for progressive outer retinal necrosis includes optimization of cART and IV anti-VZV therapy that includes combinations of systemic antivirals (acyclovir or ganciclovir plus foscarnet), frequently with twice-weekly intravitreal injections of ganciclovir and/or foscarnet (**AIII**). Adjunctive retinal surgery is sometimes recommended, along with corticosteroids and/or low-dose aspirin (**BIII**). Acute retinal necrosis can be treated with IV acyclovir for 10 to 14 days, followed by prolonged (i.e., 4–6 weeks) oral treatment (**AIII**).
- Alternatives to oral acyclovir in older adolescents include valacyclovir and famciclovir (**AI\***).
- The treatment of choice for acyclovir-resistant VZV is IV foscarnet for 7 days (**AII\***) or until no new lesions for at least 48 hours (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

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