

Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV



Developed by the Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the HHS Panel on Opportunistic Infections in Children with and Exposed to HIV—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

How to Cite the Pediatric Opportunistic Infection Guidelines:

Panel on Opportunistic Infections in Children with and Exposed to HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV. Department of Health and Human Services. Available at <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection>. Accessed (insert date) [insert page number, table number, etc., if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (<https://clinicalinfo.hiv.gov/>).

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Bacterial Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

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 (≥ 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/mm³ if ≥ 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[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Panel's Recommendations

I. What is the preferred antifungal treatment for oropharyngeal candidiasis (OPC) in children with HIV infection?

- Uncomplicated OPC infection can be effectively treated with topical therapy using clotrimazole troches or nystatin suspension for 7 to 14 days (**strong, moderate**).
- Oral fluconazole for 7 to 14 days is recommended for moderate or severe OPC disease (**strong, high**).
- For fluconazole-refractory OPC, itraconazole oral solution is recommended, although itraconazole is less well tolerated than fluconazole (**strong, moderate**).
- Chronic suppressive therapy is usually unnecessary; if it is required, fluconazole 3 times weekly is recommended (**strong, high**).

II. What is the preferred antifungal treatment for esophageal candidiasis in children with HIV infection?

- Systemic therapy is always required for esophageal disease (**strong, moderate**).
- Oral fluconazole is recommended for 14 to 21 days, but amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin) can be used in patients who cannot tolerate oral therapy (**strong, moderate**).
- For refractory esophageal disease, oral therapy can include itraconazole solution or voriconazole for 14 to 21 days (**strong, low**).
- Suppressive therapy with fluconazole 3 times weekly is recommended for recurrent infection (**strong, moderate**).

III. What is the preferred antifungal treatment for invasive candidiasis in children with HIV infection?

- In moderately severe to severely ill children with invasive candidiasis, an echinocandin is recommended. In less severely ill children who have not had previous azole therapy, fluconazole is recommended (**strong, moderate**).
- Alternatively, an initial course of amphotericin B therapy can be administered for invasive candidiasis with careful transition to fluconazole therapy to complete the treatment course (**strong, moderate**).
- Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate) or who are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**weak, moderate**).
- Children with candidemia should be treated for ≥ 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 (**strong, low**).
- Central venous catheters should be removed when feasible in children with candidemia (**strong, moderate**).

Rating System

Strength of Recommendation: Strong; Weak

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

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/mm³ or <15%, even if immune reconstitution is achieved with cART (BIII).

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

Rating of Evidence: I = One or more randomized trials in children[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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Cryptococcosis (Last updated November 6, 2013; last reviewed November 6, 2013)

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 ≥ 1 year) can be considered for asymptomatic children aged ≥ 6 years with CD4 counts ≥ 100 cells/mm³ and an undetectable viral load on ≥ 3 months of combination antiretroviral therapy (CIII). Secondary prophylaxis should be reinitiated if the CD4 count decreases to < 100 cells/mm³ (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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Cytomegalovirus

Updated: August 3, 2023

Reviewed: August 3, 2023

Panel's Recommendations

I. Is there an indication for cytomegalovirus (CMV) antibody testing in children with asymptomatic HIV (versus not testing) to guide clinical management?

- CMV antibody testing is recommended at age 1 year (or at baseline evaluation if age >1 year at initial visit) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 T lymphocyte [CD4] cell count <100 cells/mm³ or CD4 percentage <10%) (**strong, low**).

II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not screening)?

- Testing for congenital CMV infection in the first 21 days of life is recommended for infants with vertically transmitted HIV (**strong, low**). CMV testing is also suggested for all infants exposed to HIV since their HIV status will be indeterminate during the first 21 days of life when congenital CMV infection can be diagnosed (**weak, low**). Infants with confirmed congenital CMV infection should be evaluated regularly for early detection of hearing loss and appropriate intervention.

III. Is primary prophylaxis against CMV recommended for children with HIV who are CMV-seropositive (versus not providing prophylaxis)?

- Primary prophylaxis against CMV disease is not recommended for children with HIV who are not severely immunocompromised (**strong, moderate**). CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 count >100 cells/mm³ in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years (**strong, moderate**).
- Prophylaxis with valganciclovir may be appropriate for CMV-seropositive children with HIV who are severely immunosuppressed (i.e., CD4 count <50 cells/mm³ in children aged ≥6 years, or CD4 percentage <5% in children aged <6 years) (**weak, low**).
- Cessation of primary prophylaxis can be considered when the CD4 count is sustained at >100 cells/mm³ for children ≥6 years of age, or CD4 percentage >10% in children <6 years (**weak, low**).

IV. In CMV-seropositive children with HIV age <5 years, is routine ophthalmologic examination recommended to screen for CMV retinitis (versus not providing routine ophthalmologic examination)?

- Children with HIV aged <5 years who are CMV infected and severely immunosuppressed (i.e., CD4 count <50 cells/mm³ or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months (**strong, low**). As CMV retinitis can occur in patients with higher CD4 counts, ophthalmologic screening can be considered for young children with lesser degrees of immunosuppression who are unable to report visual symptoms.

V. Among children with HIV and CMV disease, is treatment with anti-CMV antiviral agents in addition to ART (versus ART alone) associated with higher rates of remission, decreased mortality, or both?

- Treatment with antiviral therapy against CMV in addition to ART is recommended for CMV disease in children with HIV (**strong, moderate**). Intravenous (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, and CNS disease). Transition from IV ganciclovir to oral valganciclovir can be considered for patients who improve on IV therapy (**strong, moderate**).

- Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV (**strong, moderate**).
- Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease (**weak, very low**).

VI. Is secondary prophylaxis after treatment of CMV disease (versus no secondary prophylaxis) recommended in severely immunocompromised children with HIV?

- After induction therapy, secondary prophylaxis (chronic maintenance therapy) is recommended for most forms of CMV disease until immune reconstitution or, in the absence of immune reconstitution, for the remainder of a patient's life. Regimens for chronic suppression include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir (**strong, moderate**).
- Secondary prophylaxis (chronic maintenance therapy) is not routinely recommended for CMV gastrointestinal disease but should be considered if relapses occur (**expert opinion**). A role for secondary prophylaxis (maintenance therapy) for CMV pneumonitis also has not been established.

VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children with HIV who have well-controlled HIV (versus continuation of secondary prophylaxis)?

- Discontinuation of secondary prophylaxis may be considered for children who are receiving ART and have a sustained (e.g., >6 months) increase in CD4 count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 count to >100 cells/mm³ for children aged ≥6 years (**weak, low**).
- All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy (secondary prophylaxis) has been discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for immune reconstitution uveitis (**strong, low**).
- Secondary prophylaxis discontinued in children with HIV because of immune reconstitution should be resumed when the CD4 percentage decreases to <15% in those aged <6 years and when the CD4 count decreases to <100 cells/mm³ in those aged ≥6 years (**strong, moderate**).

Rating System

Strength of Recommendation: Strong or Weak

Quality of Evidence: High, Moderate, Low, or Very Low

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.

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

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

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- α), IFN-2a or IFN-2b, is recommended for treating chronic HBV infection with compensated liver disease in HIV- uninfected children aged ≥ 2 years to <12 years who warrant treatment **(AI)**. IFN- α 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 ≥ 12 years **(AI)**. IFN- α 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- α 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- α 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 ≥ 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 ≥ 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 reinstituted (BIII).

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

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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 **(AIII)**.
- 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)**.

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

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Herpes Simplex Virus (Last updated June 27, 2018; last reviewed June 27, 2018)

Panel's Recommendations

I. Will condoms (compared with not using condoms) prevent herpes simplex virus (HSV) infection in sexually active adolescents and young adults with HIV?

- Condoms should be used to prevent HSV infection (and other sexually transmitted diseases) in adolescents and young adults with HIV (**strong; low**).

The data regarding the level of protection provided by condoms are very limited for individuals with HIV in general, and for youth specifically.

II. Will adolescents and young adults with HIV who have recurrent, genital HSV infection benefit from suppressive anti-HSV antiviral therapy (compared with not using suppressive therapy)?

- Adolescents and young adults with HIV who suffer severe, frequent, and/or troubling recurrent genital HSV infection will benefit from anti-HSV suppression therapy (**strong; moderate**).

III. Should children and adolescents with HIV who have severe primary or recurrent HSV (genital or orolabial) infection receive intravenous (IV) acyclovir (compared with receiving oral antiviral therapy)?

- Children and youth with HIV who have severe mucocutaneous HSV infections should be treated with IV acyclovir. When improvement is noted, they can be switched to oral therapy until healing is complete (**strong; moderate**).

IV. Should children and adolescents with HIV be treated with oral acyclovir, valacyclovir, or famciclovir for non-severe primary episodes or recurrent episodes of orolabial or genital HSV (compared with no antiviral therapy)?

- Oral anti-HSV drugs will shorten the duration and reduce the severity of non-severe HSV infections in children and adolescents with HIV. Oral valacyclovir and famciclovir have superior pharmacokinetic profiles compared with oral acyclovir (**strong; moderate**).

V. Is foscarnet the best choice for anti-HSV therapy for children and adolescents with HIV in whom therapy is failing because of acyclovir-resistant HSV?

- Foscarnet is the therapy of choice for acyclovir-resistant HSV (**strong, very low**). Ideally, the viral isolate should be tested to determine the antiviral resistance pattern.

Rating System

Strength of Recommendation: Strong; Weak

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

Histoplasmosis (Last updated November 6, 2013; last reviewed November 6, 2013)

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/mm³ 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 ≥ 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/mm³ in children aged ≥ 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[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

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 [2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors](#).
- 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.

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

Rating of Evidence: I = One or more randomized trials in children[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Isosporiasis (Cystoisosporiasis) (Last updated February 8, 2019; last reviewed February 8, 2019)

Panel's Recommendations
<p>I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of isosporiasis (cystoisosporiasis)?</p> <ul style="list-style-type: none"> Careful hand washing and thorough washing of fruits and vegetables are recommended to prevent exposure. Travelers to isosporiasis-endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables (expert opinion). <p>II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat isosporiasis (cystoisosporiasis)?</p> <ul style="list-style-type: none"> Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in children with HIV infection (strong, high). Supportive care, including replenishment of fluids and electrolytes, should be provided (expert opinion). <p>III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of isosporiasis (cystoisosporiasis)?</p> <ul style="list-style-type: none"> Antiretroviral therapy (ART) administered to children with HIV infection to reverse or prevent severe immunodeficiency may be effective in preventing recurrence of isosporiasis (weak, very low). In children with severe immunosuppression, treatment of isosporiasis should be followed by secondary prophylaxis with TMP-SMX (strong, high). <p>IV. In children with HIV infection receiving secondary prophylaxis for isosporiasis (cystoisosporiasis), when can secondary prophylaxis be safely discontinued?</p> <ul style="list-style-type: none"> Clinicians may consider discontinuing secondary prophylaxis in patients without evidence of active <i>Isospora</i> infection who have sustained improvement in immunologic status (CDC immunologic category 1 or 2) for >6 months in response to ART (weak, very low).
<p>Rating System</p> <p><i>Strength of Recommendation:</i> Strong; Weak</p> <p><i>Quality of Evidence:</i> High; Moderate; Low; or Very Low</p>

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 ≥ 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 ≥ 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[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Microsporidiosis (Last updated December 15, 2016; last reviewed December 15, 2016)

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 January 8, 2019; last reviewed January 8, 2019)

Panel's Recommendations	
I.	<p>Is prophylaxis for <i>Mycobacterium avium</i> complex (MAC), with either clarithromycin, azithromycin, or rifabutin, indicated in children with HIV infection who have advanced immunosuppression to prevent MAC infection?</p> <ul style="list-style-type: none"> Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV infection who have advanced immunosuppression (strong, low) <ul style="list-style-type: none"> Children aged <1 year: <750 cells/mm³ Children aged 1 to <2 years: <500 cells/mm³ Children aged 2 to <6 years: <75 cells/mm³ Children aged ≥6 years: <50 cells/mm³ For children who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC, although drug interactions and lack of efficacy data in children limit its use (weak, very low).
II.	<p>In children with HIV infection aged ≥2 years on stable antiretroviral therapy (ART) for ≥6 months and experiencing sustained (>3 months) CD4 T lymphocyte (CD4) cell count recovery, is discontinuation of primary prophylaxis associated with risk of disseminated MAC infection?</p> <ul style="list-style-type: none"> Primary prophylaxis can be discontinued in children with HIV infection aged ≥2 years receiving stable antiretroviral therapy (ART) for ≥6 months and experiencing sustained (>3 months) CD4 count recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults, >100 cells/mm³ for children aged ≥6 years [strong, high]; and >200 cells/mm³ for children aged 2 to <6 years [strong, moderate]).
III.	<p>In children with HIV infection and MAC disease, is testing MAC isolates for susceptibility indicated to guide management?</p> <ul style="list-style-type: none"> Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (strong, very low).
IV.	<p>In children with HIV infection and MAC disease, does combination therapy with a minimum of 2 drugs compared with monotherapy prevent or delay the emergence of resistance?</p> <ul style="list-style-type: none"> Combination therapy with a minimum of 2 drugs (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (strong, moderate). Monotherapy is associated with the emergence of high-level drug resistance.
V.	<p>In children with HIV infection and MAC disease, does the use of clarithromycin (as compared to azithromycin) improve clearance of bacteremia?</p> <ul style="list-style-type: none"> There are insufficient data to recommend the use of clarithromycin over azithromycin. Some experts use clarithromycin as the preferred first agent, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern (strong, low).
VI.	<p>In children with HIV infection and MAC disease who are treated with combination therapy, does the addition of a third agent provide improved clearance of infection?</p> <ul style="list-style-type: none"> Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial (weak, very low). Some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen, particularly in the absence of ART and in the presence of high mycobacterial counts; however, with such combination therapy, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted (strong, very low). 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.
VII.	<p>In patients with HIV infection and MAC infection who are antiretroviral naive, what is the optimal timing to start ART to prevent IRIS?</p> <ul style="list-style-type: none"> In patients with HIV and disseminated MAC disease who have not been previously ART treated, or are not receiving effective

ART initiation, ART generally should be withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce the risk of drug interactions and complications associated with IRIS and to lower the pill burden (**weak, very low**).

VIII. In patients with HIV infection and MAC infection who have failed treatment (defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment) is there an indication to repeat susceptibility testing to help guide clinical management?

- 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 (**strong, very low**). Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone.

IX. In children with HIV infection with disseminated MAC and continued immunosuppression, does secondary prophylaxis prevent recurrence of infection?

- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (**strong, low**). Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.

X. In children with HIV infection with disseminated MAC and sustained CD4 recovery, is discontinuation of secondary prophylaxis associated with risk of relapse?

- Some experts recommend discontinuation of therapy in children with HIV infection 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 ART (i.e., ART 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/mm³ for children aged ≥ 6 years [**strong, low**] and >200 cells/mm³ for children aged 2 to <6 years [**weak, very low**]).

Rating System

Strength of Recommendation: Strong; Weak

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

Mycobacterium tuberculosis

Updated: September 14, 2023

Reviewed: September 14, 2023

Panel's Recommendations	
I.	<p>Among children <15 years old with HIV, do interferon-gamma release assays (IGRAs) compared to tuberculin skin test (TST) reliably identify latent tuberculosis (TB) infection (LTBI)?</p> <ul style="list-style-type: none">• IGRAs and TSTs can be used to diagnose LTBI in children 5 years or older (strong, moderate). IGRAs are preferred for diagnosing LTBI in Bacille Calmette-Guerin–vaccinated people and those who are not likely to return for interpretation of TST results (strong, moderate).• Centers for Disease Control and Prevention (CDC) currently recommends TSTs for diagnosing LTBI in children 2–5 years old (strong, low); some experts and the American Academy of Pediatrics (AAP) Red Book recommend using IGRAs to diagnose LTBI in children ≥2 years old (strong, low).• CDC and the AAP Red Book recommend TSTs for diagnosing LTBI in children <2 years old (expert opinion).• Younger age (<5 years), HIV infection itself, and lower CD4 T lymphocyte (CD4) cell counts have been associated with indeterminate IGRA results and false negative TST results.
II.	<p>Among children <15 years old with HIV, does a negative TST or IGRA reliably exclude TB infection or disease?</p> <ul style="list-style-type: none">• Neither TST nor IGRA results definitively exclude LTBI or TB disease. Therefore, testing for LTBI with TST or IGRA should not replace regular screening questions to ascertain exposures to TB disease and presence of clinical, epidemiologic, and social risk factors for LTBI or TB disease in addition to HIV infection (strong, moderate).
III.	<p>Among children <15 years old with HIV, does LTBI treatment result in fewer cases of TB disease, compared to no treatment?</p> <ul style="list-style-type: none">• LTBI treatment is highly effective for preventing TB disease. Therefore, after TB disease (also referred to as “active TB disease”) has been excluded, children with HIV should receive treatment for LTBI as soon as possible after a positive TST or IGRA result and presumptive LTBI treatment after exposure to infectious TB (regardless of whether the child has a negative TST or IGRA result or was previously treated for TB) (strong, high).
IV.	<p>Among children <15 years old with HIV, does a 12-dose combination of once-weekly isoniazid and rifapentine in place of 9 months of daily isoniazid result in comparable outcomes for TB prevention?</p> <ul style="list-style-type: none">• Clinical trials have demonstrated that LTBI treatment with a 12-dose combination of once-weekly isoniazid and rifapentine has similar efficacy to 9 months of daily isoniazid for preventing TB disease; in practice, treatment adherence with the 12-dose regimen might be higher, resulting in higher real-world effectiveness. Therefore, the 12-dose regimen of once-weekly isoniazid and rifapentine for treatment of LTBI can be used in adults and children ≥2 years old with HIV who are on antiretroviral regimens with acceptable drug–drug interactions with rifapentine (strong, moderate).
V.	<p>Among children <15 years old with HIV and exposure to a person with drug-resistant TB, would 9 months of daily isoniazid compared to other regimens result in fewer cases of TB disease?</p> <ul style="list-style-type: none">• Some studies have demonstrated successful prevention of presumed drug-resistant TB through treatment of LTBI with regimens informed by the drug-susceptibility test (DST) results of the presumed source case.• After exposure to TB caused by isoniazid mono-resistant organisms, preventive therapy with 4 months of daily rifampin is recommended for children with HIV. Adjustment of antiretroviral therapy to consider drug–drug interactions between rifampin and antiretroviral therapy (ART) might be necessary (expert opinion).

- VI. Among children <15 years old with HIV who are diagnosed with TB while not yet on ART, does early initiation of ART (2–8 weeks) compared to delayed ART initiation result in improved treatment outcomes?
- Children with HIV who are diagnosed with non–central nervous system (CNS) TB disease and who are not yet receiving ART should be evaluated for early ART initiation, preferably within 2 to 8 weeks of starting TB therapy (**strong, moderate**).
 - Children with HIV who are diagnosed with CNS TB disease, including TB meningitis, should be evaluated for ART initiation within 2 to 8 weeks (**expert opinion**).
- VII. Among children <15 years old with HIV diagnosed with TB disease, does therapy administered by directly observed therapy (DOT) or administered by self or family members result in improved medication adherence?
- Daily DOT (by a trained health care worker) should be used to maximize adherence and minimize treatment failures, relapse rates, and emergence of acquired drug resistance (**strong, moderate**).
- VIII. Among children <15 years old with HIV who are diagnosed with intrathoracic TB disease (e.g., pulmonary or intrathoracic lymph nodes), does treatment with a four-drug regimen during the 2-month intensive phase compared to a three-drug regimen during the 2-month intensive phase result in better treatment outcomes? Among children <15 years old with HIV who are diagnosed with TB disease and treated with a four-drug regimen during the 2-month intensive phase, does a 7-month continuation phase using isoniazid and rifampin or a 4-month continuation phase using isoniazid and rifampin result in better treatment outcomes?
- In children with HIV, the recommended treatment for drug-susceptible TB is a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive phase, followed by a ≥ 4 -month continuation phase using only daily isoniazid with daily rifampin (**strong, moderate**) and adjusting of ART as required for drug–drug interactions (**expert opinion**).
 - For children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB, some experts would consider a standard three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase followed by a ≥ 4 -month continuation phase using only isoniazid and rifampin (**expert opinion**).
- IX. Among children <15 years old with HIV who are taking isoniazid or cycloserine, should adjunctive pyridoxine supplementation versus no adjunctive pyridoxine supplementation be recommended routinely to improve clinical outcomes?
- Pyridoxine supplementation (1–2 mg/kg body weight/day, maximum 50 mg/day) is recommended for all children with HIV who are taking isoniazid or cycloserine (**expert opinion**).
- X. Among children <15 years old with HIV in whom TB disease is diagnosed, what evidence-based antiretroviral treatment regimens result in better treatment outcomes?
- Among children >20 kg, dolutegravir (DTG)-based ART (dose increased to 50 mg twice daily) is preferred during TB treatment because DTG-based regimens are associated with better HIV treatment outcomes in the absence of TB (**strong, moderate**). Twice-daily DTG is safe and has favorable pharmacokinetic parameters in children >20 kg when co-administered with rifampin (**strong, moderate**).
 - Children <20 kg receiving raltegravir (RAL)-based ART who begin TB treatment should increase RAL dose to 12 mg/kg twice daily for the duration of TB treatment. Among children <20 kg who are receiving lopinavir (LPV)/ritonavir-based ART regimens, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (**strong, moderate**). Alternately, children <20 kg can receive an efavirenz (EFV)-based regimen (**expert opinion**).
 - If the EFV-based regimen is used, CYP2B6-516 genotype-directed EFV dosing is recommended.
- XI. Among children <15 years old with HIV who are diagnosed with extrapulmonary TB disease, does TB treatment for 12 months compared to standard 9-month treatment result in better treatment outcomes?
- For children with extrapulmonary disease caused by drug-susceptible TB involving the bones or joints, CNS, or disseminated/miliary disease, the recommended duration of treatment is ≥ 12 months (**expert opinion**).
- XII. Among children <15 years old with HIV who are diagnosed with TB meningitis (TBM), does the standard four-drug TB regimen compared to a regimen using ethionamide result in better treatment outcomes?

- For TBM, while DST results are pending, ethionamide can replace ethambutol (or an injectable aminoglycoside) as the fourth drug because of its superior cerebrospinal fluid penetration (**expert opinion**).
- For TBM, some experts recommend adding a fluoroquinolone to the treatment regimen pending the results of DST (**expert opinion**).

XIII. Among children <15 years old with HIV who are diagnosed with TBM, pericardial or pleural effusion, airway compression, or severe immune reconstitution inflammatory syndrome, does adjunctive treatment with corticosteroids result in improved clinical outcomes?

- Adjunctive corticosteroids (with concurrent treatment for TB disease) should be considered for children with TBM (**strong, moderate**). Adjunctive corticosteroids should also be considered in the context of severe immune reconstitution inflammatory syndrome, airway compression, pleural effusion, or pericarditis (**expert opinion**).

XIV. Among children <15 years old who are diagnosed with MDR-TB disease, does the use of individualized treatment regimens based on DST results compared to a standardized regimen result in better treatment outcomes?

- Whenever possible, treatment regimens for MDR-TB should be individualized (**expert opinion**); considerations include phenotypic and molecular DST results for the child or the presumed source case (when results of DST results are not available for the child) (**strong, moderate**). Expert consultation should be obtained for clinical management of suspected and laboratory-confirmed MDR-TB (i.e., resistance to both isoniazid and rifampin) (**expert opinion**).
- For treatment of drug-resistant TB, a minimum of five drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs (**strong, moderate**). Fluoroquinolones can be used to treat MDR-TB in children (**strong, moderate**).
- For treatment of TB that is resistant only to isoniazid, isoniazid should be discontinued, and the patient should be treated with 6 to 9 months of a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol, and levofloxacin or moxifloxacin) (**expert opinion**).

XV. Among children <15 years old with HIV who are receiving treatment for TB disease, does liver chemistry testing at 2-week intervals during the first 2 months of treatment compared to less frequent monitoring result in better clinical outcomes?

- Routine monitoring of liver enzymes is not necessary in children who have no risk factors for hepatotoxicity. For children with additional risk factors (such as concomitant ART), routine monitoring of liver enzymes should be performed before initiation and 2, 4, and 8 weeks after starting TB treatment (the same monitoring schedule as for ART initiated while a patient is receiving treatment for TB) (**expert opinion**). Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, or more frequently if clinically indicated (**expert opinion**).
- Mild elevations in serum transaminase concentration (i.e., less than five times the upper limit of normal) do not require drug discontinuation in children who are asymptomatic and in whom other findings (including bilirubin) are normal (**expert opinion**).

XVI. Among children <15 years old who are diagnosed with TB disease, does routine HIV testing compared to HIV testing and counseling upon request identify more cases of HIV?

- All people diagnosed with TB disease should be tested for HIV (**expert opinion**).

Rating System

Strength of Recommendation: Strong; Weak

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

***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 ≥ 6 years who have CD4 T lymphocyte (CD4) cell counts <200 cells/mm³ or CD4 percentage $<15\%$, for children aged 1 to <6 years with CD4 counts <500 cells/mm³ 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 (**A**).
- Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone (**A**) 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 Respirgard II® 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 ≥ 6 months, CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 200 cells/mm³ for patients aged ≥ 6 years (**BII**) and CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 500 cells/mm³ 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 reinstituted if the age-specific criteria for prophylaxis are reached (**BIII**).

Treatment

- TMP-SMX, administered IV, is the recommended treatment for PCP (**A**). 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 (**A**).
- 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[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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Syphilis

Updated: October 6, 2013

Reviewed: January 24, 2022

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 the 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 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

Rating of Evidence: I = One or more randomized trials in children[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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Toxoplasmosis (Last updated October 29, 2015; last reviewed October 29, 2015)

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/mm³ 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/mm³ 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 (AI).
- 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*). Please refer to <http://www.daraprimdirect.com> for information regarding access to pyrimethamine. If pyrimethamine is unavailable clinicians may substitute trimethoprim-sulfamethoxazole, dosed according to age and weight, in place of the combination of sulfadiazine, pyrimethamine, and leucovorin.
- 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*). Please refer to <http://www.daraprimdirect.com> for information regarding access to pyrimethamine. If pyrimethamine is unavailable clinicians may substitute trimethoprim-sulfamethoxazole dosed according to age and weight.

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

Rating of Evidence: I = One or more randomized trials *in children*[†] 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*[†] 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*[†] 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*[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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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 ≥ 200 cells/mm³) 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 zoster
 should 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

Rating of Evidence: I = One or more randomized trials in children[†] 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[†] 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[†] 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[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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