Published in final edited form as:

Pediatr Infect Dis J. 2013 December ; 32(12): 1303–1307. doi:10.1097/INF.000000000000080.

Executive Summary: 2013 Update of the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children

George K. Siberry, MD, MPH¹, Mark J. Abzug, MD², and Sharon Nachman, MD³ on behalf of the Panel on Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children*

¹Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

²Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado ³Department of Pediatrics, Stony Brook Children's Center, Stony Brook, New York

Abstract

This executive report provides an overview of the 2013 update of the Department of Health and Human Services (DHHS) Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children in the United States. The full text of the guidelines is available online at www.aidsinfo.nih.gov and as a supplement to the *Pediatric Infectious Disease Journal*. These guidelines are intended for use by clinicians and other health-care workers providing medical care for HIV-exposed and HIV-infected children in the United States. A separate document providing recommendations for prevention and treatment of OIs among HIV-infected adults and postpubertal adolescents (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents) was prepared by a working group of adult HIV and infectious disease specialists and is also available at www.aidsinfo.nih.gov.

The guidelines were developed by a panel of specialists in pediatric HIV infection and infectious diseases (the Panel on Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children) from the U.S. government and academic institutions, under the auspices of the NIH Office for AIDS Research (OAR). For each OI, one or more pediatric specialists with subject-matter expertise reviewed the literature for new information since the last guidelines were published (2009) and then proposed revised recommendations for review by the full Panel. After these reviews and discussions, the guidelines underwent further revision, with review and approval by the Panel, followed by review by CDC subject matter experts, and final review and endorsement by NIH, CDC, the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Disease Society (PIDS),

*Pediatric Opportunistic Infections Working Group Panel Members:

Leadership Group: George K Siberry, MD, MPH (Executive Secretary), Mark J. Abzug, MD (Co-Chair), Sharon Nachman, MD (Co-Chair), Beverly Bohannon, MS, RN, Michael T. Brady, MD, Kenneth L. Dominguez, MD, MPH, Edward Handelsman, MD, Lynne M. Mofenson, MD and Steve Nesheim, MD

Expert Contributors (alphabetically): Debika Bhattacharya, MD, Diana Clarke, Pharm.D., Jennifer C. Esbenshade, MD, MPH, Kathryn M. Edwards, MD, Patricia Flynn, MD, Aditya Gaur, MD, Francis Gigliotti, MD, Gail Harrison, MD, Charlotte Victori Hobbs, MD, David Kimberlin, MD, Martin B. Kleiman, MD, Emilia H. Koumans, MD, MPH, Andrew Kroger, MD, MPH, Myron J. Levin, MD, Cara L. Mack, MD, Ben Marais, MD, Gabriela Maron, MD, James McAuley, MD, MPH, Heather J. Menzies, MD, MPH, Anna-Barbara Moscicki, MD, Michael Narkewicz, MD, Richard Rutstein, MD, Jane Seward, MD, Masako Shimamura, MD, William J. Steinbach, MD, Gregory J. Wilson, MD.

and the American Academy of Pediatrics (AAP). Treatment of OIs is an evolving science, and availability of new agents or clinical data on existing agents may change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated. Interim updates to recommendations will be posted on the www.aids.nih.gov website as needed and the full guidelines document will continue to be reviewed and updated every 2–3 years. Consultation with an expert in the management of HIV infection and OIs in children is also encouraged.

Major recommendations are accompanied by ratings that include a letter that indicates the strength of the recommendation and a Roman numeral that indicates the quality of the evidence supporting the recommendation (TABLE 1); this rating system is similar to the rating systems used in other USPHS/IDSA guidelines. Because licensure of drugs for children and their application in clinical care often relies on efficacy data from adult trials in combination with pharmacokinetic, safety, and observational data in children, recommendations sometimes rely on data from clinical trials or studies in adults with supporting data in children. Thus, the quality of evidence level is accompanied by an asterisk (*) to indicate that evidence supporting the recommendation is a hybrid of higher-quality adult study evidence and consistent but lower-quality pediatric study evidence. This modification to the rating system is the same as that used by the DHHS Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.

The guidelines discuss opportunistic illnesses that occur in the United States and ones that might occur during international travel, such as malaria. Because the guidelines target HIV-exposed and -infected children in the United States, the opportunistic pathogens discussed are those common to the United States and do not include certain pathogens such as *Penicillium marneffei* that may be seen almost exclusively outside the United States. They also do not include pathogens that are common but seldom cause chronic infection, or that have the same risk, disease course, and approach to prevention and treatment in all children regardless of HIV status. Topic areas covered for each OI include a brief description of the epidemiology, clinical presentation, and diagnosis of the OI in children; prevention of exposure; prevention of first episode of disease; discontinuation of primary prophylaxis after immune reconstitution; treatment of disease; monitoring for adverse effects during treatment, including immune reconstitution inflammatory syndrome (IRIS); management of treatment failure; prevention of disease recurrence; and discontinuation of secondary prophylaxis after immune reconstitution. The most important, rated recommendations are highlighted in boxed major recommendations sections preceding the text for each OI, and a table of dosing recommendations follows the text for each OI. The tables at the end of the document summarize recommendations for dosing of medications used for prevention and treatment of OIs in children; drug preparation and toxicity information for children; and major drug-drug interactions. Vaccination recommendations for HIV-infected children and adolescents are summarized in the section entitled “Preventing Vaccine-Preventable Diseases in HIV-Infected Children and Adolescents” and individual OI sections and detailed in figures at the end of the document.

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

In the era before development of potent combination antiretroviral treatment (cART) regimens, opportunistic infections (OIs) were the primary cause of death in HIV-infected children². Current ART regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial and dramatic decrease in AIDS-related OIs and deaths in both adults and children^{3–6}.

Despite this progress, prevention and treatment of OIs remain critical components of care for HIV-infected children. HIV-associated OIs and other related infections continue to occur in HIV-infected children^{4,16}. OIs continue to be the presenting symptom of HIV infection among children whose HIV-exposure status is unknown because of lack of maternal antenatal HIV testing. For infants and children with known HIV infection, barriers such as inadequate medical care, lack of availability of suppressive antiretroviral (ARV) regimens in the face of extensive prior treatment and drug resistance, caregiver substance abuse or mental illness, and multifactorial adherence difficulties may hinder effective HIV treatment and put them at risk of OIs even in the ART era. These same barriers may then impede provision of primary or secondary OI prophylaxis to children for whom such prophylaxis is indicated. In addition, the addition of concomitant OI prophylactic drugs may only exacerbate the existing difficulties in adhering to ART. Multiple drug-drug interactions of OI, ARV, and other compounds that result in increased adverse events and decreased treatment efficacy may limit the choice and continuation of both cART and prophylactic regimens. Finally, immune reconstitution inflammatory syndrome (IRIS), initially described in HIV-infected adults but also seen in HIV-infected children, can complicate treatment of OIs when cART is started or when optimization of a failing regimen is attempted in patients with acute OIs. Thus, preventing and treating OIs in HIV-infected children remains important even in the cART era.

The Need for Specific Prevention and Treatment Guidelines for Children

Mother-to-child transmission is an important mode of acquisition of HIV infection and of OIs in children. HIV-infected women coinfecting with opportunistic pathogens may be more likely than HIV-uninfected women to vertically transmit these infections to their infants. For example, higher rates of perinatal transmission of hepatitis C and cytomegalovirus (CMV) have been reported from HIV-infected than from HIV-uninfected women^{12,13}. In addition, HIV-infected women or HIV-infected family members coinfecting with certain opportunistic pathogens may be more likely to transmit these infections horizontally to their children, increasing the likelihood of primary acquisition of such infections in young children. For example, *Mycobacterium tuberculosis* infection in children primarily reflects acquisition from family members who have active tuberculosis (TB) disease, and increased incidence and prevalence of TB among HIV-infected individuals is well documented. HIV-exposed or -infected children in the United States may have a higher risk of exposure to *M. tuberculosis* than would comparably aged children in the general U.S. population because of residence in households with HIV-infected adults¹⁴. Furthermore, HIV-infected women may have reduced transplacental transfer of antibodies that protect their infants against serious bacterial infections than women without HIV infection¹⁵. Therefore, these guidelines for treatment and prevention of OIs consider both HIV-infected and HIV-uninfected children born to HIV-infected women.

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

Data related to the efficacy of various therapies for OIs in adults are often extrapolated to children, but issues related to drug pharmacokinetics, formulation, ease of administration,

and dosing and toxicity require special considerations for children. Young children, in particular, metabolize drugs differently from adults and older children, and the volume of distribution differs. Unfortunately, data often are lacking on appropriate drug dosing recommendations for children aged <2 years.

Immune Reconstitution Inflammatory Syndrome

ART improves immune function and CD4 cell count in HIV-infected children as in adults; within the first few months after starting treatment, HIV viral load sharply decreases and the CD4 T lymphocyte count rapidly increases. This results in increased capacity to mount inflammatory reactions. After initiation of cART, in some patients, reconstitution of the immune system produces a worsening of symptoms of an existing active OI (paradoxical IRIS) or the appearance of new symptoms of a latent or occult OI (unmasking IRIS), where infectious pathogens previously not recognized by the immune system now evoke an immune response. This inflammatory response often is exaggerated in comparison with the response in patients who have normal immune systems. The pathologic process of IRIS is inflammatory and not microbiologic in etiology. Thus, distinguishing IRIS from treatment failure is important. In therapeutic failure, a microbiologic culture should reveal the continued presence of an infectious organism, whereas in paradoxical IRIS, follow-up cultures most often are sterile. However, with “unmasking” IRIS, viable pathogens may be isolated.

In children, the conditions most commonly associated with IRIS include mycobacterial infections, herpes zoster, herpes simplex virus, and cryptococcal infection. In addition, reactions related to bacille Calmette-Guérin (BCG) vaccine have been one of the most common IRIS manifestations in children in low-resource settings.^{18,19,21} IRIS is uncommon in children in the United States. No randomized controlled trials have been published evaluating treatment of IRIS in children. Disease-specific information and recommendations for managing IRIS are included in individual sections, as appropriate.

Initiation of cART for an Acute OI in Treatment-Naïve Children

Specific data regarding when to start cART in children with an acute OI and how to manage cART when an acute OI occurs in a child already receiving cART are limited. The benefit of initiating cART is improved immune function, which could result in faster resolution of the OI. This is particularly important for OIs for which effective therapeutic options are limited or not available, such as microsporidiosis, progressive multifocal leukoencephalopathy, and Kaposi sarcoma (KS). However, potential problems exist when cART and treatment for the OI (eg, rifampicin-based anti-tuberculous therapy) are initiated simultaneously. These include drug-drug interactions between the ARV and antimicrobial drugs, particularly given the more limited repertoire of ARV drugs available for children than for adults; issues related to toxicity, including potential additive toxicity of ARV and OI drugs and difficulty in distinguishing cART toxicity from OI treatment toxicity; and the potential for IRIS to complicate OI management. IRIS is more likely to occur in patients with advanced HIV infection and higher OI-specific antigenic burdens, such as those who have disseminated infections or a shorter time from acute OI onset to start of cART. Most IRIS events have potential to result in significant morbidity but do not result in death; the exception is OIs with CNS involvement, the form of IRIS most commonly associated with mortality²³.

The primary consideration in delaying cART until after initial treatment of the acute OI is risk of additional illness or death during the delay. Although the short-term risk of death in the United States during a 2-month cART delay may be relatively low, mortality in resource-limited countries is significant. Randomized trials in adults demonstrate significantly better outcomes when adults with non-CNS OIs begin cART early in the course

of OI treatment, but raise concern for potential increased mortality when cART is initiated early in adults (in Africa) with cryptococcal meningitis^{24–26}. In the absence of trials in children, recommendations about timing of cART initiation in children undergoing OI treatment are not definitive and management should be individualized and made in consultation with a specialist with expertise in managing HIV and OIs in children. The timing is a complex decision based on the severity of HIV disease, efficacy of standard OI-specific treatment, social support system, medical resource availability, potential drug-drug interactions, and risk of IRIS. Most experts believe that the early benefit of potent cART outweighs any increased risk to children who have OIs such as microsporidiosis, PML, or KS for which effective treatment is lacking.

Change in OI sections and section with major updates

The updated guidelines have added new sections for influenza, *Giardia* and (*Cysto*)*Isospora*, while the sections on *Bartonella*, *Aspergillus* and human herpes virus (HHV)-6 and HHV-7 have been eliminated. These changes reflect trends in the types of illnesses that presently require clinician management and expertise. The major changes for each section, and the subject matter expert(s) who led the updates to that section, are summarized in Table 2.

References

1. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Aug 11. 2011 p. 1-268. Available at <http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>. 2011. Available at
2. Dankner WM, Lindsey JC, Levin MJ. Pediatric ACTGPT. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J*. Jan; 2001 20(1):40–48. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11176565>. [PubMed: 11176565]
3. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. Nov 22; 2001 345(21):1522–1528. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11794218>. [PubMed: 11794218]
4. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. Jul 19; 2006 296(3):292–300. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16849662>. [PubMed: 16849662]
5. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986–2004. *Pediatrics*. Jul; 2007 120(1):100–109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17606567>. [PubMed: 17606567]
6. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr*. Jan; 2010 53(1):86–94. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20035164>. [PubMed: 20035164]
7. CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *MMWR*. 1995; 44(RR-8):1–34. Available at.
8. CDC. Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons - 2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR*. 2002; 51(RR-08):1–46. Available at.
9. CDC. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *MMWR Recomm Rep*. Jun 27; 1997 46(RR-12):1–46. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9214702>.
10. CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR*. 1999; 48(RR-10):1–59. Available at.

11. Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *Clin Infect Dis*. Feb 1; 2005 40 (Suppl 1):S1–84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15655768>. [PubMed: 15655768]
12. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology*. Aug; 2001 34(2):223–229. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11481604>. [PubMed: 11481604]
13. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med*. Jul 8; 1999 341(2):77–84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10395631>. [PubMed: 10395631]
14. Gutman LT, Moye J, Zimmer B, Tian C. Tuberculosis in human immunodeficiency virus-exposed or -infected United States children. *Pediatr Infect Dis J*. Nov; 1994 13(11):963–968. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7845749>. [PubMed: 7845749]
15. Jones CE, Naidoo S, De Beer C, Esser M, Kampmann B, Hesselning AC. Maternal HIV infection and antibody responses against vaccine-preventable diseases in uninfected infants. *JAMA*. Feb 9; 2011 305(6):576–584. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21304083>. [PubMed: 21304083]
16. Kourtis AP, Bansil P, Posner SF, Johnson C, Jamieson DJ. Trends in hospitalizations of HIV-infected children and adolescents in the United States: analysis of data from the 1994–2003 Nationwide Inpatient Sample. *Pediatrics*. Aug; 2007 120(2):e236–243. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17606535>. [PubMed: 17606535]
17. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. Apr 10; 2009 58(RR-4):1–207. quiz CE201–204. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19357635>.
18. Wang ME, Castillo ME, Montano SM, Zunt JR. Immune reconstitution inflammatory syndrome in human immunodeficiency virus-infected children in Peru. *Pediatr Infect Dis J*. Oct; 2009 28(10):900–903. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19687769>. [PubMed: 19687769]
19. Smith K, Kuhn L, Coovadia A, et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS*. Jun 1; 2009 23(9):1097–1107. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19417581>. [PubMed: 19417581]
20. Puthanakit T, Oberdorfer P, Ukarapol N, et al. Immune reconstitution syndrome from nontuberculous mycobacterial infection after initiation of antiretroviral therapy in children with HIV infection. *Pediatr Infect Dis J*. Jul; 2006 25(7):645–648. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16804438>. [PubMed: 16804438]
21. Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J*. Jan; 2006 25(1):53–58. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16395104>. [PubMed: 16395104]
22. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clin Infect Dis*. Jun 1; 2006 42(11):1639–1646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16652323>. [PubMed: 16652323]
23. Torok ME, Kambugu A, Wright E. Immune reconstitution disease of the central nervous system. *Curr Opin HIV AIDS*. Jul; 2008 3(4):438–445. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19373003>. [PubMed: 19373003]
24. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009; 4(5):e5575. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19440326>. [PubMed: 19440326]
25. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25; 2010 362(8):697–706. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20181971>. [PubMed: 20181971]

26. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. Jun 1; 2010 50(11):1532–1538. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20415574>. [PubMed: 20415574]

Table 1

System for grading strength of recommendations and quality of supporting evidence

Strength of Recommendation	Quality of Evidence for Recommendation [^]
A. Strong recommendation for the statement B. Moderate recommendation for the statement C. Optional recommendation for the statement	I: One or more randomized trials <u>in children</u> [†] with clinical outcomes and/or validated laboratory endpoints I*: One or more randomized trials <u>in adults</u> with clinical outcomes and/or validated laboratory endpoints with accompanying data <u>in children</u> [†] 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 <u>in children</u> [†] with long-term clinical outcomes II*: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data <u>in children</u> [†] from one or more smaller nonrandomized trials or cohort studies with clinical outcome data III: Expert opinion

[†] Studies that include children or children/adolescents but not studies limited to postpubertal adolescents.

[^] In circumstances where there is level I or level II evidence from studies in adults with accompanying data in children that come only from non-randomized trials or cohort studies with clinical outcomes, experts assigned a rating of I* or II*, respectively, if they judged the evidence from children sufficient to support findings from adult studies. In circumstances where there is level I or level II evidence from studies in adults with no or almost no accompanying data in children, experts assigned a rating of III.

Major changes since 2009 in the 2013 update of the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children

TABLE 2

OPPORTUNISTIC ILLNESS	MAJOR CHANGES IN 2013 UPDATE	PRINCIPAL AUTHOR(S)	CO-AUTHOR(S)
<i>Bacterial infections</i>	<ul style="list-style-type: none"> Stronger recommendation for discontinuation of antibiotic for primary or secondary SBI prophylaxis in children with sustained immune reconstitution Updated recommendations for immunizations against bacterial infections 	<i>George K. Siberry, MD, MPH</i>	
<i>Candidal infections</i>	<ul style="list-style-type: none"> Fluconazole, echinocandins or amphotericin B preferred and itraconazole no longer preferred for initial treatment of Candida esophagitis Voriconazole or itraconazole recommended for fluconazole-refractory Candida esophagitis Echinocandins preferred for severely ill children with candidemia 	<i>William J. Steinbach, MD</i>	
<i>Coccidioidomycosis</i>	<i>No major changes</i>	<i>Martin B. Kleiman, MD</i>	
<i>Cryptococcal infections</i>	<ul style="list-style-type: none"> Newer formulations of amphotericin B included in recommended treatment of cryptococcal central nervous system (CNS) disease 	<i>Aditya Gaur, MD</i>	<i>Patricia Flynn, MD</i>
<i>Cryptosporidium Infections</i>	<i>No major changes</i>	<i>Patricia Flynn, MD</i>	<i>Gabriela Maron, MD</i>
<i>Cytomegalovirus infections</i>	<ul style="list-style-type: none"> Expansion of valganciclovir prophylaxis option for severely immunocompromised, CMV seropositive children to those under age 6 years Limited expansion of recommended use of valganciclovir for treatment of CMV disease in children. 	<i>Masako Shimamura, MD</i>	<i>David Kimberlin, MD</i>
<i>Giardiasis (NEW section)</i>	<ul style="list-style-type: none"> Emphasis on role of cART in prevention and management of giardiasis Timidazole or nitazoxanide recommended as preferred, and metronidazole as alternative, treatment of giardiasis 	<i>Patricia Flynn, MD</i>	<i>Gabriela Maron, MD</i>
<i>Hepatitis B Virus (HBV) Infection</i>	<ul style="list-style-type: none"> Expansion down to age 2 years of the use of tenofovir disoproxil fumarate in cART regimens for HIV-HBV coinfecting children who require treatment for both infections 	<i>Michael Narkewicz, MD</i>	<i>Cara L. Mack, MD</i> <i>Debika Bhattacharya, MD</i>
<i>Hepatitis C Virus (HCV) Infection</i>	<ul style="list-style-type: none"> Recommendation for evaluation to confirm or exclude HCV infection in infants born to HCV-infected mothers 	<i>Cara L. Mack, MD</i>	<i>Michael Narkewicz, MD</i> <i>Debika Bhattacharya, MD</i>
<i>Herpes Simplex Virus infections</i>	<i>No major changes</i>	<i>Myron J. Levin, MD</i>	

OPPORTUNISTIC ILLNESS	MAJOR CHANGES IN 2013 UPDATE	PRINCIPAL AUTHOR(S)	CO-AUTHOR(S)
<i>Histoplasmosis</i>	<ul style="list-style-type: none"> Choice of formulation of amphotericin B for non-CNS histoplasmosis based on cost, availability and tolerability. Liposomal amphotericin B remains the preferred formulation for CNS disease. 	<i>Martin B. Kleiman, MD</i>	
<i>Human Herpesvirus 8 infections</i>	<i>No major changes</i>	<i>Richard Rutstein, MD</i>	
<i>Human Papillomavirus infections</i>	<ul style="list-style-type: none"> Expansion of routine HPV vaccine recommendation to HIV-infected females and males ages 11–26 years old 	<i>Anna-Barbara Moscicki, MD</i> <i>Sharon Nachman, MD</i>	
<i>Immunizations</i>	<ul style="list-style-type: none"> Summarized in Figs. 1 and 2 Updated recommendations for Haemophilus influenza type b, meningococcal, tetanus-diphtheria-acellular pertussis, human papillomaviruses, measles-mumps-rubella and pneumococcal vaccines 	<i>Andrew Kroger, MD, MPH</i>	<i>Jane Seward, MD</i>
<i>Influenza (NEW section)</i>	<ul style="list-style-type: none"> Recommendations for prevention and anti-viral treatment of influenza in HIV-infected children 	<i>Kathryn M. Edwards, MD</i>	<i>Jennifer C. Esbenshade, MD, MPH</i> <i>Gregory J. Wilson, MD</i>
<i>Isosporiasis (Cystoisosporiasis) (NEW section)</i>	<ul style="list-style-type: none"> Emphasis on cART to reduce HIV-related risk of (cysto)isporiasis Strong recommendation for trimethoprim-sulfamethoxazole to treat (cysto)isporiasis 	<i>Patricia Flynn, MD</i>	<i>Gabriela Maron, MD</i>
<i>Malaria</i>	<ul style="list-style-type: none"> Expanded guidance on drug interactions between antiretroviral and antimalarial drugs 	<i>Charlotte Victori Hobbs, MD</i> <i>Sharon Nachman, MD</i>	
<i>Microsporidiosis</i>	<i>No major changes</i>	<i>Patricia Flynn, MD</i>	<i>Gabriela Maron, MD</i>
<i>Mycobacterium avium Complex Disease</i>	<i>No major changes</i>	<i>James McAuley, MD, MPH</i>	
<i>Mycobacterium tuberculosis infections</i>	<ul style="list-style-type: none"> Updated recommendations for use of interferon-gamma release assays (IGRA) for diagnosis of latent tuberculosis in children Change to preference for early (within 2–8 weeks of starting anti-TB therapy) cART initiation for children not already receiving cART 	<i>Ben Marais, MD</i>	<i>Heather J. Menzies, MD, MPH</i>
<i>Pharmacology review</i>	<ul style="list-style-type: none"> Expanded guidance on toxicities of drugs used for prevention and treatment of opportunistic illnesses (Table 4) Expanded information on drug interactions and additional resources for drug interaction data (Table 5) 	<i>Diana Clarke, Pharm. D.</i>	
<i>Pneumocystis Pneumonia</i>	<i>No major changes</i>	<i>Francis Gigliotti, MD</i>	
<i>Progressive Multifocal Leukoencephalopathy</i>	<i>No major changes</i>	<i>Gail Harrison, MD</i>	
<i>Syphilis</i>	<ul style="list-style-type: none"> Updated based on 2010 CDC Sexually Transmitted Diseases Treatment Guidelines 	<i>Emilia H. Koumans, MD, MPH</i>	

OPPORTUNISTIC ILLNESS	MAJOR CHANGES IN 2013 UPDATE	PRINCIPAL AUTHOR(S)	CO-AUTHOR(S)
<i>Toxoplasmosis</i>	<i>No major changes</i>	<i>James McAuley, MD, MPH</i>	
<i>Varicella-Zoster Virus (VZV) infections</i>	<ul style="list-style-type: none"> Updated recommendations for prophylaxis after exposure to VZV (more selective indications; role of acyclovir) 	<i>Myron J. Levin, MD</i>	
<i>Opportunistic Illness Topics Eliminated Since 2009 Guidelines: Bartonella; Aspergillus; Human Herpesvirus 6 and 7.</i>			