# 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)

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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/).

# Table of Contents

# What's New in the Guidelines

**Updated:** September 14, 2023
**Reviewed:** September 14, 2023

The *Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV* (Pediatric Opportunistic Infection Guidelines) document is published in an electronic format that can be updated easily as relevant changes in prevention and treatment recommendations occur.

The editors and subject-matter experts are committed to timely changes in this document because many health care providers, patients, and policy experts rely on this source for vital clinical information.

All changes are developed by the subject-matter groups listed in the document (changes in group composition also are posted promptly). These changes are reviewed by the editors and by relevant outside reviewers before the document is altered.

## September 14, 2023

### *Mycobacterium tuberculosis*

- Added recommendations for dolutegravir- and raltegravir-based antiretroviral (ARV) regimens in the context of tuberculosis (TB) disease for children >20 kg and <20 kg, respectively.
- Added references to American Academy of Pediatrics (AAP) guidance that recommends interferon-gamma release assays (IGRAs) to diagnose latent tuberculosis infection (LTBI) in children ≥2 years old.
- Added recommendations that children ≥2 years old with HIV infection who are receiving ARV regimens with acceptable drug-drug interactions with rifapentine can receive the 12-dose isoniazid-rifapentine LTBI treatment regimen.

## August 8, 2023

### *Introduction*

- Summarized key changes resulting from a rescoping consultation for the Pediatric Opportunistic Infection Guidelines in 2021 to better address the current needs of clinicians caring for children with and exposed to HIV.
- Updated the context and description for the use of the previous and new evidence rating systems.
- Combined the previous *Summary* and the *Background and Recommendations Rating Scheme* sections into a single *Introduction* section to streamline essential information and consolidate reference tools in one accessible location.

## Cytomegalovirus

- Added a recommendation to test infants exposed to HIV for congenital cytomegalovirus (CMV) infection due to high rates of CMV transmission among newborns with and exposed to HIV.
- Harmonized congenital CMV treatment recommendations for infants with HIV to match those for children without HIV based on American Academy of Pediatrics Red Book guidelines.

# Introduction

**Updated:** January 09, 2024
**Reviewed:** January 09, 2024

The *Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV*, hereafter referred to as "the guidelines," are intended for use by clinicians and other health care workers providing medical care for children with HIV and children who were HIV exposed but uninfected (HEU) in the United States. The guidelines are developed by the Panel on Opportunistic Infections in Children with and Exposed to HIV (the Panel), which is composed of specialists in pediatric HIV infection and infectious diseases. The guidelines discuss opportunistic infections (OIs) that occur in the United States and OIs that might be acquired during international travel, such as malaria. This report incorporates changes in the guidelines after receiving recommendations from a consultation of pediatric infectious diseases and HIV experts in 2021 to rescope the guidelines and align prioritization of section revisions with the evolving pediatric HIV landscape.

A list of acronyms that are commonly used throughout the guidelines can be found in Appendix A. Key to Acronyms. Other guideline considerations appear in Appendix B. Important Guidelines Considerations, which includes a description of the composition and organizational structure of the Panel, definition and management of conflicts of interest, funding sources for the guidelines, public commentary, and plans for updating the guidelines. The names and financial disclosures for each of the panel members are listed in Appendix C. Panel Roster and Appendix D. Financial Disclosures, respectively. Appendix E. Archived Sections provides access to the last updated versions of sections that are no longer being reviewed by the Panel: Human Herpesvirus 8 Disease, Influenza, and Progressive Multifocal Leukoencephalopathy. A separate document, the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*, is prepared by a panel of adult HIV and infectious disease specialists and provides recommendations for the prevention and treatment of OIs among adults and postpubertal adolescents with HIV.

## Opportunistic Infections in the Era of Antiretroviral Therapy

### *Children with HIV*

In the era before potent combination antiretroviral (ARV) regimens, OIs were the primary cause of death in children with HIV.[1] Current ARV regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial decrease in AIDS-related OIs and deaths in both adults and children.[2-7]

Despite this progress, prevention and treatment of OIs remain critical components of care for children with HIV. OIs continue to be the presenting symptoms of HIV among children whose HIV exposure status is unknown, usually because of a lack of maternal antenatal HIV testing or unrecognized acquisition of HIV during childhood. For infants and children with known HIV, various barriers may hinder effective HIV treatment and put them at risk of OIs, even in the antiretroviral therapy (ART) era. Such barriers include inadequate medical care, lack of availability of suppressive ARV regimens in the face of extensive prior treatment and drug resistance, caregiver substance abuse or mental illness, and multifactorial adherence difficulties. These same barriers may then impede provision of primary or secondary OI prophylaxis to infants and children for whom such prophylaxis is indicated. In addition, concomitant OI prophylactic drugs may only exacerbate the existing difficulties in adhering to ART. Multiple drug–drug interactions among OI drugs, antiretrovirals, and treatment for other conditions that result in increased frequency of adverse events and decreased treatment efficacy may limit the choice and continuation of both ART and prophylactic regimens. Finally, immune reconstitution inflammatory syndrome (IRIS), initially described in adults with HIV but also seen in children with HIV, can complicate treatment of OIs when ART is started or when optimization of a failing regimen is attempted in patients with acute OIs. Thus, prevention and treatment of OIs in children with HIV remain important, even in the combination ART era.

## *Infants Exposed to HIV*

An important mode of childhood acquisition of OIs and HIV is from mothers with HIV. Women with HIV may be more likely to have coinfections with opportunistic pathogens (e.g., hepatitis C) and more likely than women without HIV to transmit these infections to their infants. In addition, mothers or other family members with HIV who are coinfected with certain opportunistic pathogens may be more likely to transmit these infections horizontally to children in their care, resulting in increased likelihood of primary acquisition of such infections in young children.[8] Furthermore, transplacental transfer of antibodies that protect infants against serious infections may be lower in women with HIV than in women without HIV.[9] Therefore, infections with opportunistic pathogens may affect not just infants with HIV but also infants who were HEU. These guidelines for treating OIs in children, therefore, consider treatment of infections in all children born to people with HIV, whether or not perinatal transmission to the infant occurred.

## *Antiretroviral Therapy*

HIV-related immunodeficiency remains the major risk factor for most of the infections that are discussed in this document, and the prevention or reversal of HIV-related immunodeficiency with combination ART is a key part of prevention and management of OIs in general. Recommendations for combination ART in children in the United States are developed and regularly updated by a separate panel of pediatric HIV experts (see the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*). In the United States, it has become standard practice for all children with HIV to be treated with combination ART (see What to Start in the Pediatric Antiretroviral Guidelines). Therefore, the Panel has framed its OI prevention and treatment recommendations on the expectation that children are already receiving or preparing to start combination ART.

## *Opportunistic Infection Treatment Recommendations*

The most important prevention and treatment recommendations are highlighted in boxed major recommendations preceding each section, and a table of dosing recommendations appears at the end of each section. The guidelines conclude with summary tables that display dosing recommendations for all the conditions, drug toxicities, and drug interactions, as well as a figure describing immunization recommendations for children and adolescents aged 0 to 18 years.

Because treatment of OIs is an evolving science and availability of new agents or clinical data on existing agents may change therapeutic options and preferences, these recommendations will be periodically updated and will be available on the ClinicalInfo website.

## History of the Guidelines

In 1995, the U.S. Public Health Service and the Infectious Diseases Society of America (IDSA) developed guidelines for preventing OIs in adults, adolescents, and children with HIV.[6] These guidelines, developed for health care providers and their patients with HIV, were revised in 1997, 1999, and 2002.[10-12] In 2001, the National Institutes of Health (NIH), IDSA, and Centers for Disease Control and Prevention (CDC) convened a working group to develop guidelines for treating HIV-associated OIs, with a goal of providing evidence-based guidelines on treatment and prevention. In recognition of unique considerations for infants, children, and adolescents with HIV—including differences between adults and children in mode of acquisition, natural history, diagnosis, and treatment of HIV-related OIs—a separate pediatric OI guidelines writing group was established. The Pediatric Opportunistic Infection Guidelines were initially published in December 2004.[13] In 2009, recommendations for preventing and treating OIs in children with HIV and children who are HEU were updated and combined into one document; a similar document on preventing and treating OIs in adults and adolescents with HIV, prepared by a separate group of adult HIV and infectious diseases specialists, was developed at the same time. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the NIH Office of AIDS Research (OAR). Since 2009, the Pediatric Opportunistic Infection Guidelines have been managed as a living document on the internet. Each section is reviewed periodically and updated as needed—based on the literature published in the interim—by a panel of pediatric specialists with expertise in specific OIs.

In 2021, the Panel, again under the auspices of OAR, convened a panel of 45 pediatric infectious diseases, HIV, and related subject-matter experts for a formal consultation on rescoping the pediatric OI guidelines so that they would better reflect the current pediatric HIV milieu. Following their consultation, several important recommendations that affect the scope and revision process have been adopted in the current guidelines, including the following: prioritizing revisions of each topic or OI section based on emerging epidemiology; archiving of OIs with low frequencies; adding a consolidated section on parasites, diarrheal disease, and/or travel; and discontinuing the use of modified GRADE in favor of a rating system that aligns with that of other NIH OAR HIV Clinical Guidelines.

## Unique Considerations

### *Sexual Maturity Rating*

These guidelines are a companion to the *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*.[14] Clinicians providing care for adolescents are advised to use the Adult and Adolescent Opportunistic Infection Guidelines for guidance on the care of postpubertal adolescents (sexual maturity rating [SMR] 4 and 5) and the Pediatric Opportunistic Infection Guidelines for guidance on the care of adolescents at SMR 3 or lower (see Table 1 below).

**Table 1. Sexual Maturity Rating**

| GIRLS | | |
|---|---|---|
| **Breast Development** | **Stage** | **Pubic Hair Growth** |
| Prepubertal; nipple elevation only | 1 | No pubic hair |
| Small, raised breast bud | 2 | Sparse growth of hair along labia |
| General enlargement and raising of breast and areola | 3 | Darkening, coarsening, and curling, increase in amount |
| Further enlargement with projection of areola and nipple as secondary mound | 4 | Hair resembles adult type, but not spread to medial thighs |
| Mature, adult contour, with areola in same contour as breast, and only nipple projecting | 5 | Adult type and quantity, spread to medial thighs |
| **BOYS** | | |
| **Genital Development** | **Stage** | **Pubic Hair Growth** |
| Prepubertal; no change in size or proportion of testes, scrotum, and penis from early childhood | 1 | No pubic hair |
| Enlargement of scrotum and testes; reddening and change in texture in skin of scrotum; little or no penis enlargement | 2 | Sparse growth of hair at base of penis |
| Increase first in length then width of penis; growth of testes and scrotum | 3 | Darkening, coarsening, and curling, increase in amount |
| Enlargement of penis with growth in breadth and development of glans; further growth of testes and scrotum, darkening of scrotal skin | 4 | Hair resembles adult type, but not spread to medial thighs |
| Adult size and shaped genitalia | 5 | Adult type and quantity, spread to medial thighs |

Source: Tanner JM. Growth at adolescence. Oxford: Blackwell Scientific Publications, 1962.

## *HIV Disease Staging*

CD4 T lymphocyte (CD4) cell count and CD4 percentage are well-established measures of immune status in HIV infection. HIV disease stage—and risk of OI—is categorized based on age-specific CD4 counts and CD4 percentages.[15] Note that CD4 thresholds for young children (≤5 years old) are different than those for older children (≥6 years old), adolescents, and adults (see Table 2 below). Historically, CD4 percentage was more commonly used in studies of children with HIV because CD4 percentages have less age-related variation, while CD4 counts normally decline with increasing age;

furthermore, studies that characterized OI risk and evaluated prevention and treatment interventions were not consistent in the CD4 values they used. As a result, the evidence supporting OI recommendations is presented according to the CD4 values used in the relevant studies, but, in many cases, the recommendations will be adjusted to reflect the current thresholds for CD4-defined HIV disease stages. In addition, if the recommendation is expressed in terms of CD4 count, then a footnote may be used to indicate the corresponding CD4 percentages and vice versa.

**Table 2. HIV Infection Stage* Based on Age-Specific CD4 T Lymphocyte (CD4) Cell Count or CD4 Percentage of Total Lymphocytes**

| Stage | Age on Date of CD4 Test | | | | | |
|---|---|---|---|---|---|---|
| | <1 year | | 1–5 years | | ≥6 years | |
| | Cells/mm$^3$ | % | Cells/mm$^3$ | % | Cells/mm$^3$ | % |
| 1 | ≥1,500 | ≥34 | ≥1,000 | ≥30 | ≥500 | ≥26 |
| 2 | 750–1,499 | 26–33 | 500–999 | 22–29 | 200–499 | 14–25 |
| 3 | <750 | <26 | <500 | <22 | <200 | <14 |

* The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only if the count is missing. If a stage 3–defining opportunistic illness has been diagnosed (see MMWR 2014 Appendix), then the stage is 3 regardless of CD4 test results.

Modified from: Centers for Disease Control and Prevention: 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(No. RR-12); and Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR.* 2014;63(No. RR-3):1-10.

## *Evidence Rating System*

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation includes a letter (A, B, or C) that represents the strength of the recommendation, and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation. The recommendation is accompanied, as needed, by explanatory text that reviews the evidence and the Panel's assessment. The letters A, B, and C represent the strength of the recommendation for or against a preventive or therapeutic measure and are based on assessing the balance of benefits and risks of adhering compared to not adhering to the recommendation. Roman numerals I, I*, II, II*, and III indicate the quality of evidence supporting the recommendation and are based on study design. Roman numerals with asterisks describe types of evidence in which a higher quality of evidence exists for adults than for children (see Table 3). More detailed information on this rating system can also be seen in the Supplemental Information section below.

The modified GRADE evidence rating scheme, originally adapted from IDSA in 2015, has been discontinued in accordance with the rescoping recommendations in 2021 to better align with the NIH OAR guideline formats. For more background about guidelines development from IDSA, see the *IDSA Handbook on Clinical Practice Guideline Development*. During this transition period away from the modified GRADE scheme, it was critical to ensure completion of sections undergoing the guidelines revision process during the consultation, and thus, there will be guideline sections published with the previous modified GRADE approach. The modified GRADE rating scheme can be found in the Supplemental Information section below.

## Table 3. Recommendations Rating System

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

*† Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents*

*Note: In circumstances where there is level I or level II evidence from studies in adults with accompanying data in children that come only from small, nonrandomized 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.*

## Supplemental Information

### *Current Recommendations Rating System*

**Strength of Recommendation Rating A—Strong.** The benefit associated with adhering to the recommendation nearly always outweighs the risk of not adhering to the recommendation. The recommendation applies to most patients in most circumstances and should be adhered to by clinicians unless there exists a compelling rationale for an alternative approach.

**Strength of Recommendation Rating B—Moderate.** The benefit associated with adhering to the recommendation often outweighs the risks of not adhering to the recommendation but not as frequently as a recommendation with an A rating. The recommendation applies to many patients in some circumstances.

**Strength of Recommendation Rating C—Optional.** It is unclear whether the benefits associated with adhering to the recommendation outweigh the risks of not adhering to the recommendation; other alternatives may be equally reasonable.

**Quality of Evidence Rating I—Randomized Clinical Trial Data.** Quality of Evidence Rating I will be used if there are data from large, randomized trials in children with clinical and/or validated laboratory endpoints. **Quality of Evidence Rating I*** will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and substantial pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. A rating of I* may be used for quality of evidence if, for example, a randomized Phase III clinical trial in adults demonstrates that a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

**Quality of Evidence Rating II—Nonrandomized Clinical Trials or Observational Cohort Data.** In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data from high-quality nonrandomized clinical trials or observational cohort studies may be used if there are sufficient pediatric data consistent with the adult studies. Quality of Evidence Rating II will be used if there are data from well-designed, nonrandomized trials or observational cohorts in children. **Quality of Evidence Rating II*** will be used if there are well-designed, nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. A rating of II* may be used for quality of evidence if, for example, a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 count and data from smaller observational studies in children indicate that a similar CD4 count is associated with clinical benefit.

**Quality of Evidence Rating III—Expert Opinion.** Where neither clinical trial nor observational data exist, we rely on expert opinion.

## *Previous Recommendations Rating System*

### Modified GRADE Process for Evidence Review for Pediatric OI Guideline Recommendations

1. *Expert authors make a list of recommendations/topics to consider for recommendations in the revision.*
2. *Each potential recommendation is turned into a "PICO" question.* PICO questions specify Population of interest, Intervention being considered, Comparison intervention or condition, and Outcomes of interest. For example: Would treatment of [population] children with HIV with [intervention] intravenous immune globulin (IVIG), [comparison] compared to no IVIG, prevent [outcomes] serious bacterial infections or death?
3. *A systematic literature review is conducted to assemble the available evidence that pertains to the PICO question*. In collaboration with an NIH librarian, a literature search is conducted using a standardized "search strategy." The initial literature search in 2015 extended back to January 2013 and has been updated thereafter with new publications from the search strategy about every 6 months. Peer-reviewed literature is preferred for evidence, but meeting abstracts can be used on a case-by-case basis.
4. *For each PICO question, the evidence is reviewed and the quality of the evidence rated in a TABLE.* The template for these tables is provided below. *These tables will be posted on the guidelines website, with links from the corresponding OI section, but will not be integrated into the OI section document.* These tables will make it easier for readers to understand the sources and quality of underlying evidence that supports the recommendations.

   *Note:* If there is high-quality evidence from clinical trials that informs a recommendation, observational and smaller studies can be omitted from the summary table.

   *Note:* If an evidence-based guideline (e.g., by CDC or IDSA) has already made a rated recommendation that applies to children with HIV, then that existing guideline can be referenced without repeating the evidence review and summary.

   a. The *quality of evidence* reflects the extent to which the confidence in findings is adequate to support a particular recommendation. GRADE offers four levels for the quality of evidence: high, moderate, low, and very low.
   b. The quality of evidence is determined by the following process:
      i. Basic study design: randomized, controlled trials generally start as high quality; observational studies start as low quality (moderate, if large and well designed).
      ii. Quality is downgraded for risk of bias, imprecise estimates, inconsistency, and indirectness (including evidence from adult studies applied to children).
      iii. Quality is upgraded for large effect size and dose-response gradient, or if likely biases would reduce apparent effect.
5. *The text of the recommendation is composed.* Each PICO question should have at least one recommendation (unless the conclusion following evidence review is that a recommendation was not warranted). Recommendations are written with unambiguous language and clearly defined terms. Information that contains areas of uncertainty or controversy is documented within the

recommendation. Specific subpopulation variability and exceptions are noted in the recommendations.

*Note:* For strong recommendations, the appropriate wording is "recommend" or "should" and for weak recommendations, "suggest" or "consider."

6. *The recommendation is assigned a strength: strong or weak*. The strength of recommendation reflects the extent to which one can be confident that the desirable consequences of an intervention outweigh the undesirable ones.
7. *An overall rating of quality of evidence is assigned: high, moderate, low, and very low*. This rating is based on the evidence reviewed in the Table, which may contain studies of varying quality.

   *Note:* If an evidence-based guideline (e.g., by CDC or IDSA) has already made a rated recommendation that applies to children with HIV, then the recommendation and its same/analogous rating are taken from the other guideline.
8. *A brief overall narrative is written that synthesizes how the available evidence supports the recommendation.* This narrative is based on the evidence table with an effort to avoid repeating detailed descriptions of each study. When multiple trials have yielded similar, noncontroversial results, a single sentence with appropriate references may suffice. Long, descriptive paragraphs of the methodology and findings of individual trials are discouraged. *This narrative will appear in the body of the document, immediately after the recommendation.*

   *Note:* If an evidence-based guideline (e.g., by CDC or IDSA) has already made a rated recommendation that applies to children with HIV, there will be one sentence that indicates that the recommendation is based on the review and assessment of the guideline used.
9. *Table of Dosing Recommendations*

## TEMPLATE for PICO Questions for Evidence Summary and Rating of Quality

| PICO Question & Tabular EVIDENCE SUMMARY | | | | | | | |
|---|---|---|---|---|---|---|---|
| Question: | | | | | | | |
| Search terms*: | | | | | | | |
| Reference | Study design (N) | Patient characteristics | Intervention | Comparison | Outcome measures | Main findings | Evidence quality:<br>1. Begin with basic study design. Generally, randomized clinical trials start as high quality; observational studies start as low quality (moderate, if large and well designed). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 2. Downgrade for risk of bias, imprecise estimates, inconsistency, and indirectness (including evidence from adult studies applied to children).<br>3. Upgrade for large effect size and dose-response gradient, or if likely biases would reduce apparent effect. |

* Search terms can be placed at top of document, instead of in individual tables, if they apply to all evidence tables in your section.

## mGRADE Organization and Format of Each Topic Section

1. *Box*

   Clinical "PICO" questions with accompanying rated recommendations

2. *Introduction/Overview*

   Brief discussion of epidemiology, clinical presentation, diagnosis, prevention, and treatment of each pathogen

3. *Rated recommendations and supporting evidence narratives for each prevention/treatment category*

   a. Prevention/treatment categories

      i. Primary Prevention: preventing exposure; preventing first episode of disease; discontinuing primary prophylaxis

      ii. Treatment: primary treatment (of infection/disease); monitoring of treatment response and adverse events (including IRIS); management of treatment failure

      iii. Secondary Prevention: preventing recurrence; discontinuing secondary prophylaxis

   b. Within each category (e.g., preventing exposure)

      i. "PICO" question

      ii. Recommendation with strength and evidence quality rating in parentheses

         Recommendation text (strong or weak; high, moderate, low, very low)

      iii. Brief narrative discussing the recommendation and its rationale

## References


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# Preventing Vaccine-Preventable Diseases in Children and Adolescents with HIV Infection (Last updated October 25, 2019; last reviewed October 25, 2019)

Vaccines are an extremely effective primary prevention tool, and vaccines that protect against 16 diseases are recommended for routine use in children and adolescents in the United States. Vaccination schedules for children from birth through 18 years of age are published annually by the Centers for Disease Control and Prevention. For more information see:

- Recommended Child and Adolescent Immunization Schedule for Ages 18 years or Younger, United States, 2019;
- Recommended Child and Adolescent Immunization Schedule by Medical Condition, United States, 2019; *and*
- Altered Immunocompetence: General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices

These schedules are compiled from approved, vaccine-specific policy recommendations which are standardized in collaboration with the major vaccine policy-setting and vaccine-delivery organizations (i.e., the Advisory Committee on Immunization Practices [ACIP], the American Academy of Pediatrics [AAP], the American Academy of Family Physicians [AAFP], and the American College of Obstetricians and Gynecologists [ACOG]) (see the ACIP Recommendations).

Children with HIV infection should be protected from vaccine-preventable diseases. Most vaccines recommended for routine use can be administered safely to children who are exposed to or have contracted HIV. The recommended vaccination schedule for children aged 0 through 18 years who are HIV-exposed or HIV-positive corresponds to the ACIP-approved schedule for all children with ACIP-approved additions specific to children with HIV infection incorporated (see Figure 1).

All inactivated vaccines—whether killed whole organism or subunit, recombinant, toxoid, polysaccharide, or polysaccharide protein-conjugate—can be administered safely to individuals with altered immunocompetence. In addition, because of the risks of increased disease severity in children with HIV infection, specific vaccines like pneumococcal and *Haemophilus influenzae* type b conjugate vaccine are also recommended for children with HIV beyond the routinely recommended ages for healthy children (if not previously administered at routinely recommended ages in early childhood). Additional vaccines are also recommended, such as pneumococcal polysaccharide vaccine for children aged ≥2 years following receipt of pneumococcal conjugate vaccine, and MenACWY vaccine, recommended beginning at age 2 months. Other vaccines might be recommended outside the routine age window in children with HIV, including pneumococcal conjugate vaccine (PCV13), or human papillomavirus vaccine in males. Live attenuated influenza vaccine (LAIV) is **contraindicated** for children with HIV. Annual, age-appropriate influenza vaccination is recommended for children with HIV as part of routine prevention for influenza.[1] The effectiveness of any vaccine may be suboptimal in an individual with an immunocompromising condition.[2-4]

Compared to children who are immunocompetent, children with HIV are at higher risk for complications of some diseases for which only live vaccines are available. Based on limited safety, immunogenicity, and efficacy data in children with HIV, single-antigen varicella vaccine should be considered for children and adolescents with HIV infection with CD4 T lymphocyte (CD4) cell percentages ≥15%. Eligible children should receive 2 doses 3 months apart, with the first dose administered as soon as possible after the child's first birthday. Two doses of measles, mumps, and rubella (MMR) vaccine are recommended for all individuals with HIV aged ≥12 months who do not have evidence of current severe immunosuppression.[5]

Oral typhoid vaccine **should not be administered** to children with HIV.

If recommended, yellow fever vaccine (YFV) can be administered to children aged 9 months to 6 years with CD4 percentages > 24% of total lymphocytes or to children aged ≥6 years with a CD4 count of ≥500 per $mm^3$. Providers should ensure that patients do not have AIDS or other clinical manifestations of HIV, which is a contraindication.

Precautions to administering YFV vaccination should be followed and administering YFV may be considered for people with HIV aged ≥6 years with a CD4 count 200 to 499/$mm^3$ or children aged 6 months to 6 years with a CD4 percentage of 15% to 24% of total lymphocytes. Providers should ensure that patients do not have AIDS or other clinical manifestations of HIV, which is a contraindication. If international travel requirements rather than an increased risk for acquiring YFV infection are the only reason to vaccinate in someone with a precaution, the person should be excused from vaccination and issued a medical waver to fulfill health regulations.

YFV is **contraindicated** for all children aged <6 months. YFV is also **contraindicated** for all children with AIDS, other clinical manifestations of HIV, and children with CD4 counts <200 per $mm^3$ or <15% of total lymphocytes for children aged <6 years. If a person with severe immunosuppression based on CD4 counts (<200 per $mm^3$ or <15% total), AIDS, or symptomatic HIV cannot avoid traveling to an area in which yellow fever is endemic, a medical waiver should be provided and counseling on protective measures against mosquito bites should be emphasized. People who were HIV positive at the time of the initial dose of YFV should receive a booster dose every 10 years if they continue to travel or live in areas that put them at risk for yellow fever virus infection. See Yellow Book and ACIP recommendations for detailed listings of precautions and contraindications for yellow fever vaccination.

Limited data are available from clinical trials on the safety of rotavirus vaccines in infants known to have HIV infection who were clinically asymptomatic or mildly symptomatic when vaccinated.[6] The data available do not suggest that the safety profile of rotavirus vaccines in infants with clinically asymptomatic or mildly symptomatic HIV infection is different from that in infants who do not have HIV infection.[7,8] Two other considerations support rotavirus vaccination of infants exposed to or infected with HIV: first, the diagnosis of perinatal HIV infection may not be established in infants born to mothers with HIV infection before the oldest age at which the rotavirus vaccine series can be administered;[9] and second, vaccine strains of rotavirus are attenuated suggesting that if vaccine induced-disease occurred, it would be mild. Consultation with an immunologist or infectious disease specialist is advised for infants with known or suspected altered immunocompetence, such as infants with HIV infection with low CD4 percentage or counts, before rotavirus vaccine is administered.

For certain vaccines (such as hepatitis A) the response to vaccination may be greater with immune reconstitution following antiretroviral therapy (ART),[10] or there may be variation in immunogenicity based on viral load (e.g., improved immune response with lower HIV viral load), such as with YFV.[11] For most vaccines, patients with higher CD4 counts have improved immune response, which also means that response (e.g., to vaccination for influenza, MMR, yellow fever) likely would be improved after ART is initiated.[1,12,11,13] Concern about the lack of protection from vaccines administered before a child begins ART has prompted debate about the need for routine re-immunization once a child is on effective ART.[11,14] On the basis of low rates of measles seroprotection in children with HIV who received MMR before starting ART and the safety and high rates of measles seroprotection associated with MMR re-immunization once the children were receiving ART,[15] the ACIP made specific recommendations for routine MMR re-immunization after initiation of ART.[5] Individuals with perinatal HIV infection who were vaccinated prior to establishment of effective ART should receive two appropriately spaced doses of MMR vaccine once effective ART has been established, unless they are severely immunosuppressed or have other acceptable current evidence of measles immunity.[5] For some vaccines (e.g., for hepatitis B), ACIP recommends performing post-vaccination serology to ensure immune response.

Children living in a household with an adult or child with HIV can receive MMR vaccine because the viruses in this vaccine are not transmitted from person to person. All members of a household aged >6 months can receive yearly influenza vaccines. Immunization against varicella is encouraged for all household contacts of children with HIV infection with evidence of immunity to varicella.[15] Transmission of varicella vaccine virus from an immunized, immunocompetent individual to a household contact is rare.

Consult the specific ACIP statements (available at ACIP Vaccine Recommendations and Guidelines) for more detail regarding recommendations, precautions, and contraindications for use of specific vaccines (see Prevention of Pneumococcal Disease and Use of a 2-Dose Schedule for Human Papillomavirus Vaccination).[10,12,15,16-27]

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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 ≥25% if <6 years old; CD4 percentage ≥20% and CD4 count >350 cells/mm$^3$ 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* |

## Bacterial Infections, Serious and Recurrent

### *Epidemiology*

Before combination antiretroviral therapy (cART) was available, serious bacterial infections were the most commonly diagnosed opportunistic infections in HIV-infected children, with an event rate of 15 per 100 child-years.[1] Pneumonia was the most common bacterial infection (11 per 100 child-years), followed by bacteremia (3 per 100 child-years), and urinary tract infection (2 per 100 child-years). Other serious bacterial infections, including osteomyelitis, meningitis, abscess, and septic arthritis, occurred at rates <0.2 per 100 child-years. Less serious bacterial infections such as otitis media and sinusitis were particularly common (17–85 per 100 child-years) in untreated HIV-infected children.[2]

Since the advent of cART, bacterial infections in HIV-infected children have decreased substantially,[3,4] and predominate in children who have not had a sustained response to cART.[3] The rate of pneumonia has decreased to 2 to 3 per 100 child-years,[4-7] similar to the rate of 3 to 5 per 100 child-years in HIV-uninfected children.[8,9] The rate of bacteremia/sepsis during the cART era also has decreased dramatically to 0.35 to 0.37 per 100 child-years,[5,6,10] but it remains substantially higher than that of invasive pneumococcal disease in U.S. children (0.018 and 0.0022 per 100 child years for those aged <5 and 5–17-year-olds, respectively).[11] Rates of sinusitis and otitis in cART-treated children are substantially lower than in the pre-cART era (2.9–3.5 per 100 child-years), but remain higher than those in HIV-uninfected children.[6]

## *Pneumonia*

Acute pneumonia, often presumptively diagnosed in children, was associated with increased risk of long-term mortality in HIV-infected children in one study during the pre-cART era.[12] HIV-infected children not receiving cART who present with pneumonia are more likely to be bacteremic and to die than are HIV-uninfected children with pneumonia.[13] Children with chronic lung disease, including bronchiectasis, complicating repeated episodes of infectious pneumonia or lymphocytic interstitial pneumonitis,[14] are more susceptible to infectious exacerbations (similar to those in children and adults with bronchiectasis or cystic fibrosis) caused by typical respiratory bacteria (*Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*) and *Pseudomonas* spp.

## *Streptococcus pneumoniae*

*S. pneumoniae* is the most prominent invasive bacterial pathogen in HIV-infected children both in the United States and worldwide, accounting for >50% of bacterial bloodstream infections in HIV-infected children.[1,10,15-19] HIV-infected children have a markedly higher risk of pneumococcal infection than do HIV-uninfected children.[20,21] In a Philadelphia cohort, the incidence of invasive pneumococcal disease (IPD) in HIV-infected children decreased by more than 80% from 1.9 per 100 patient-years before cART to 0.3 per 100 in the cART era.[22] The rate of hospitalization for IPD in HIV-infected children and youth also declined by nearly 80% since introduction of routine use of cART and pneumococcal conjugate vaccine.[23] In children with invasive pneumococcal infections, study results vary on whether penicillin-resistant pneumococcal strains are more commonly isolated from HIV-infected than HIV-uninfected patients.[17,22,24,25] Invasive disease caused by penicillin-nonsusceptible pneumococcus was associated with longer duration of fever and hospitalization but not with greater risk of complications or poorer outcome in a study of HIV-uninfected children;[26] however, most IPD in HIV-infected children is not caused by non-susceptible pneumococci.[22] In 2010, the 7-valent pneumococcal conjugate vaccine (licensed in 2000) was replaced by a 13-valent vaccine (including coverage for serotype 19A) for routine use in all children, including HIV-infected children.[27] The impact of routine use of 13-valent conjugate vaccine on invasive pneumococcal disease in HIV-infected children is not yet known.

## *Haemophilus influenzae Type b*

HIV-infected children are at increased risk of *Haemophilus influenzae* type b (Hib) infection. In a study in South African children who had not received Hib conjugate vaccine, the estimated relative annual rate of overall invasive Hib disease in children aged <1 year was 5.9 times greater in those who were HIV-infected than those who were uninfected, and HIV-infected children were at greater risk for bacteremic pneumonia.[28] Hib infection is rare in HIV-infected children in the United States because routine Hib immunization confers direct protection to immunized HIV-infected children and herd immunity confers indirect protection.[29]

## *Neisseria meningitidis (Meningococcus)*

HIV infection is associated with an increased risk of meningococcal disease.[30,31] In a population-based study of invasive meningococcal disease in Atlanta, Georgia,[31] as expected, the annual rate of disease was higher in 18- to 24-year-olds (1.17 per 100,000) than for all adults (0.5 per 100,000), but the estimated annual rate in HIV-infected adults was substantially higher (11.2 per 100,000). There are no studies of meningococcal disease risk in HIV-infected children in the United States. However, in a population-based surveillance study in South Africa, HIV infection significantly increased the risk of meningococcal bacteremia, which was associated with increased risk of death in all ages, but especially in children. Very few HIV-infected patients were receiving cART at the time of this study.[30]

## *Methicillin-Resistant Staphylococcus aureus (MRSA)*

HIV infection appears to be a risk factor for MRSA infections in adults, but findings are conflicting about the relative contribution of immunosuppression vs. concomitant psychosocial risk factors to this increased risk.[32-34] Limited data suggest that HIV-infected children, like their uninfected counterparts, experience predominantly non-invasive, skin, and soft tissue infections as a result of community-associated MRSA strains and that greater immunosuppression may not confer greater risk of MRSA.[35]

### *Other Pathogens*

Other pathogens, including *Pseudomonas aeruginosa* and enteric organisms, cause infection in HIV-infected children, especially those who have indwelling vascular catheters or advanced immunosuppression or are not on cART.[19,29,36,37] The most commonly isolated pathogens in catheter-associated bacteremia in HIV-infected children are similar to those in HIV-negative children with indwelling catheters, including coagulase-negative staphylococci, *S. aureus*, enterococci, *P. aeruginosa*, gram-negative enteric bacilli, *Bacillus cereus*, and *Candida* spp.[18,37] In a cohort of 680 HIV-infected children in Miami, Florida, 10.6% had 95 episodes of gram-negative bacteremia between 1980 and 1997, of which only 6 were associated with an indwelling vascular catheter. The predominant organisms were *P. aeruginosa*, nontyphoidal *Salmonella*, and *Escherichia coli* (15%).[29] More than 70% had advanced immunosuppression and the overall case-fatality rate was 43%. In Kenyan children with bacteremia, HIV infection increased the risk of non-typhoidal *Salmonella* and *E. coli* infections.[36]

### *HIV-Exposed (but Uninfected) Children*

Data are conflicting about whether infectious morbidity increases in children who have been exposed to but not infected with HIV. In studies in developing countries, HIV-exposed but uninfected (HEU) infants had higher mortality (primarily because of bacterial pneumonia and sepsis) than did those born to uninfected mothers.[38,39] Advanced maternal HIV infection was associated with increased risk of infant death.[38,39] In a study in Latin America and the Caribbean, 60% of 462 HEU infants experienced infectious disease morbidity during the first 6 months of life, with the rate of neonatal infections (particularly sepsis) and respiratory infections higher than rates in comparable community-based studies.[40] However, in a study from the United States, the rate of lower respiratory tract infections in HEU children was within the range reported for healthy children during the first year of life.[41] There is increasing evidence for insufficient maternally derived antibody levels in HEU infants that put those infants at increased risk of pneumococcal and other vaccine-preventable infections.[42]

## Clinical Manifestations

Clinical presentation depends on the particular type of bacterial infection (e.g., bacteremia/sepsis, osteomyelitis/septic arthritis, pneumonia, meningitis, sinusitis/otitis media);[43] HIV-infected children with invasive bacterial infections typically have a clinical presentation similar to HIV-uninfected children.[21,44,45]

The classical signs, symptoms, and laboratory test abnormalities that usually indicate invasive bacterial infection (e.g., fever, elevated white blood cell count) are usually present but may be lacking in HIV-infected children who have reduced immune competence.[21,43] One-third of HIV-infected children not receiving cART who have acute pneumonia have recurrent episodes.[12] Bronchiectasis and other chronic lung damage that occurs before initiation of cART can predispose to recurrent pulmonary infections, even in the presence of effective cART.[14] Lower respiratory bacterial infections in children with lymphocytic interstitial pneumonitis (LIP) most often are a result of the same bacterial pathogens that cause lower respiratory infection in HIV-infected children without LIP and manifests as fever, increased sputum production, and respiratory difficulty superimposed on chronic pulmonary symptoms and radiologic abnormalities.[46]

In studies in Malawi and South Africa before the availability of cART, the clinical presentations of acute bacterial meningitis in HIV-infected and HIV-uninfected children were similar.[47,48] However, in a study from Malawi, HIV-infected children were 6.4-fold more likely to have repeated episodes of meningitis than were HIV-uninfected children, although the study did not differentiate relapses from new infections.[47] In both studies, HIV-infected children were more likely to die from meningitis than were HIV-uninfected children.

## Diagnosis

Attempted isolation of a pathogenic organism from normally sterile sites (e.g., blood, cerebrospinal fluid, pleural fluid) is strongly recommended, as identification and antimicrobial resistance testing will guide effective treatment.

Because of difficulties obtaining appropriate specimens, such as sputum, from young children, bacterial pneumonia most often is a presumptive diagnosis in children with fever, pulmonary symptoms, and an abnormal chest radiograph, unless an accompanying bacteremia exists. In the absence of a laboratory isolate, differentiating viral from bacterial pneumonia using clinical criteria can be difficult.[8] *Mycobacterium tuberculosis* (TB) and *Pneumocystis jirovecii* pneumonia (PCP) must always be considered in HIV-infected children with pneumonia. Presence of wheezing makes acute bacterial pneumonia less likely than other causes (e.g., viral pathogens, asthma exacerbation), atypical bacterial pathogens (e.g., *Mycoplasma pneumoniae*), or aspiration. Children with LIP often have episodes of bacterial respiratory infection superimposed on chronic wheezing. Sputum induction obtained by nebulization with hypertonic (5%) saline was evaluated for diagnosis of pneumonia in 210 South African infants and children (median age: 6 months), 66% of whom were HIV-infected.[49] The procedure was well-tolerated, and identified an etiology in 63% of children with pneumonia (identification of bacteria in 101, TB in 19, and PCP in 12 children). Blood and fluid from pleural effusion (if present) should be cultured.

In children with bacteremia, a source should be sought. In addition to routine chest radiographs, other diagnostic radiologic evaluations may be necessary in HIV-infected children with compromised immune systems to identify less apparent foci of infection (e.g., bronchiectasis, internal organ abscesses).[50-52] In children with suspected bacteremia and central venous catheters, blood culture should be obtained through the catheter and (if possible) peripherally; if the catheter is removed because of suspected infection, the catheter tip should be sent for culture.[53] Assays for detection of bacterial antigens or evidence by molecular biology techniques are important for diagnostic evaluation of HIV-infected children in whom unusual pathogens may be involved or difficult to identify or culture with standard techniques. For example, detection of *Bordetella pertussis* and *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* with polymerase chain reaction assays of nasopharyngeal secretions may aid in the diagnosis of these infections.[8,54,55]

## Prevention Recommendations

### *Preventing Exposure*

Because *S. pneumoniae* and *H. influenzae* (other than type b) are common in the community, no effective way exists to eliminate exposure to these bacteria. However, routine use of conjugated pneumococcal (initially 7-valent and, more recently 13-valent) and Hib vaccines in the United States has dramatically reduced vaccine-type nasopharyngeal colonization in healthy children, thus limiting the exposure of HIV-infected children to these pathogens (herd immunity).

#### Food

To reduce the risk of exposure to potential GI bacterial pathogens, health-care providers should advise that HIV-infected children avoid eating the following raw or undercooked foods (including other foods that contain them): eggs, poultry, meat, seafood (especially raw shellfish), and raw seed sprouts **(BIII)**. Unpasteurized dairy products and unpasteurized fruit juices also should be avoided **(BIII)**. Of particular concern to HIV-infected infants and children is the potential for caretakers to handle these raw foods (e.g., during meal preparation) and then unknowingly transfer bacteria from their hands to children's food, milk or formula, or directly to the children. Hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods **(BIII)**. Produce should be washed thoroughly before being eaten **(BIII)**. These precautions are especially important for children who are not receiving effective cART.

#### Pets

When obtaining a new pet, caregivers should avoid dogs or cats aged <6 months or stray animals **(BIII)**. HIV-infected children and adults should avoid contact with any animals that have diarrhea and should always wash their hands after handling pets, especially before eating, and avoid contact with pets' feces **(BIII)**. HIV-infected children should avoid contact with reptiles (e.g., snakes, lizards, iguanas, turtles) and with chicks and ducklings (as well as their uncooked eggs) because of the risk of salmonellosis **(BIII)**. These precautions are especially important for children who are not receiving effective cART.

### Travel

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

## *Preventing Disease*

### Immunization

In addition to cART, one of the most important interventions to prevent bacterial infections in HIV-infected children is to ensure that they are immunized according to the HIV-specific recommended schedule (Figures 1 and 2) **(AII)**. Vaccines that protect against bacterial pathogens directly (e.g., pneumococcal, Hib, meningococcal, pertussis) and indirectly (e.g., influenza) have been demonstrated safe and immunogenic in HIV-infected children.[56-60] HIV-infected children are at increased risk of under-immunization.[61] Status of vaccination against Hib, pneumococcus, meningococcus, pertussis, influenza, and all recommended vaccines should be reviewed at every clinical encounter and indicated vaccinations provided, according to the established recommendations for immunization of HIV-infected children **(AIII)**. Effective cART instituted before immunization offers the best means to optimize response to immunization.[62] Lack of effective cART may reduce the magnitude, quality or duration of immunologic response and likely impairs memory response. Greater number or strength of vaccine doses are recommended in some circumstances to overcome suboptimal response. Evidence is mounting that protective immunity to vaccine-preventable disease is lacking in a high proportion of perinatally HIV-infected children who received many of their immunizations before the availability of effective cART.[63] These data suggest that HIV-infected children may benefit from assessment of seroprotection and/or re-immunization for certain vaccines.

### Hib Vaccine

HEU and HIV-infected infants and children aged ≤5 years should receive Hib vaccine on the same schedule as that recommended for healthy infants, including for catch-up immunization **(AII)**. (Figure 1). Hib vaccine is recommended for routine administration to infants aged 2, 4, and 6 months (6-month dose not needed if PRP-OMP Hib conjugate vaccine used for 2- and 4-month doses), and 12 to 15 months; 1 to 3 doses are recommended for previously unvaccinated infants and children aged 7 to 23 months depending on age at first vaccination. Health-care providers should consider use of Hib vaccine for HIV-infected children aged ≥5 years who have not previously received Hib vaccine **(AIII)**. For these older children, a single dose of any Hib conjugate vaccine is recommended.[64]

### Pneumococcal Vaccines

HEU and HIV-infected infants and children aged 2 to 59 months should receive the 13-valent pneumococcal vaccine (PCV13) on the same schedule as that recommended for healthy infants and children, including series completion for those who initiated immunization with PCV7 **(AII)**.[23,65,66] A 4-dose series of PCV13 is recommended for routine administration to infants aged 2, 4, 6, and 12 to 15 months; 2 or 3 doses are recommended for previously unvaccinated infants and children aged 7 to 23 months depending on age at first vaccination.[64] Incompletely vaccinated children aged 24 to 71 months should receive 1 dose of PCV13 if 3 doses of PCV (7 or 13) were received previously, or 2 doses of PCV13 ≥8 weeks apart if <3 doses of PCV (7 or 13) were received previously. Children who have received a complete series of PCV7 should receive a supplemental dose of PCV13 if they are aged 14 through 71 months. In addition, HIV-infected children aged ≥2 years should receive 23-valent pneumococcal polysaccharide vaccine (PPSV) (≥2 months after their last PCV dose), with a single revaccination with PPSV 5 years later **(AII)**.[57,64] Data are limited regarding efficacy of PCV7 or PCV13 for children aged ≥6 years who are at high risk of pneumococcal infection. However, the U.S. Food and Drug Administration recently approved expanded use of PCV13 for children aged 6 to 17 years.[67] In addition, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recently recommended that a single dose of PCV13 be routinely administered to children aged 6 years through 18 years with immunocompromising conditions who have not previously received PCV13.[68] Therefore, a single dose of PCV13 should be routinely administered to HIV-infected children aged 6 through 18 years who did not receive PCV13 before age 6 years[64] (Figures 1 and 2). A multicenter study of pneumococcal vaccination in a group of HIV-infected children not administered PCV during infancy demonstrated the safety and immunogenicity of 2 doses of PCV7 followed by one dose of PPSV for cART-treated HIV-infected children aged 2 to 19 years (including some who had previously received pneumococcal polysaccharide vaccination [PPSV]).[57] Based on this study, some experts recommend giving 2 doses of PCV13 to HIV-infected children aged ≥6 years who never received PCV7 or PCV13 **(BII)**. PPSV may be offered ≥8 weeks after PCV13 in children aged 6 to 18 years who received a PCV13 dose after having received PPSV **(CII)**.[57] The incidence of invasive pneumococcal disease was substantially lower in HIV-infected vaccine recipients in a placebo-controlled trial of a nine-valent PCV in South African children (most whom were not receiving antiretroviral therapy), but vaccine efficacy was somewhat lower in HIV-infected (65%) than HIV-uninfected children (85%).[66]

### Meningococcal Vaccine

Like healthy children, HIV-infected children should routinely receive meningococcal conjugate vaccine (MCV) at age 11 to 12 years and again at age 16 **(AII)**. In contrast to the 1-dose primary series for healthy children, the primary series of MCV for all HIV-infected children aged ≥9 months is 2 MCV doses at least 2 months apart for children aged 2 to 10 years, and 2 to 3 months apart for children aged 9 to 23 months in order to improve rates of seroprotection **(AII)**.[64,69-71] HIV-infected children aged 9 months to 10 years who have evidence of splenic dysfunction or complement deficiency or who plan to travel to high-incidence areas should receive the primary MCV series **(AIII)**. While ACIP does not list HIV infection as a specific indication for MCV, some experts give MCV to all HIV-infected children aged 9 months to 10 years because of the potentially increased risk of meningococcal disease **(CIII)**. HIV-infected children who receive their primary MCV series at ages 9 months to 10 years and who are at ongoing increased risk of meningococcal exposure should receive another MCV dose 3 years later (if primary MCV immunization was at ages 9 months to 6 years) or 5 years later (if primary MCV immunization was at ≥7 years) **(AIII)**.[64] MCV should be repeated every 5 years in children with splenic dysfunction or complement deficiency for as long as their splenic dysfunction persists **(AIII)**.

### Influenza Vaccine

Because influenza increases the risk of secondary bacterial respiratory infections,[72] annual influenza vaccination for influenza prevention can be expected to reduce the risk of serious bacterial infections in HIV-infected children **(BIII)** (Figures 1 and 2).[73] HIV-infected children should receive annual influenza vaccination according to the HIV-specific recommended immunization schedule **(AII)**.[60,64]

### Chemoprophylaxis

Trimethoprim-sulfamethoxazole (TMP-SMX) administered daily for PCP prophylaxis may decrease the rate of serious bacterial infections (predominantly respiratory) in HIV-infected children unable to take cART **(BII)**.[16,74] Atovaquone combined with azithromycin, which provides prophylaxis for *Mycobacterium avium* complex (MAC) as well as PCP, is well tolerated and as effective as TMP-SMX in preventing serious bacterial infections in HIV-infected children.[75] However, routine use of antibiotics solely for primary prevention of serious bacterial infections (i.e., when not indicated for PCP or MAC prophylaxis or other specific reasons) promotes development of drug-resistant organisms and is not routinely recommended **(BIII)**. Intravenous immune globulin (IVIG) is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (immunoglobulin G <400 mg/dL) **(AI)**.[15]

### *Discontinuation of Primary Prophylaxis*

The Pediatric AIDS Clinical Trials Group (PACTG) 1008 demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved sustained (≥16 weeks) immune reconstitution (CD4 T lymphocyte [CD4] cell percentage >20% to 25%) while receiving ART did not result in excessive rates of serious bacterial infections.[6] HIV-infected children who are receiving an antibiotic for the purpose of primary prevention of serious bacterial infections should discontinue antibiotic prophylaxis once they have achieved sustained (i.e., ≥3 months) immune reconstitution (CD4 percentage ≥25% aged <6 years; CD4 percentage ≥20% or CD4 count >350 cells/mm$^3$ if aged ≥6 years) **(BII)**.

## Treatment Recommendations

### *Treating Disease*

The principles for treating serious bacterial infections are the same in HIV-infected and HIV-uninfected children. Specimens for microbiologic studies should be collected before initiation of antibiotic treatment. However, in patients with suspected serious bacterial infections, therapy should be administered empirically and promptly without waiting for results of such studies; therapy can be adjusted once results become available. The local prevalence of antibiotic-resistant bacteria (e.g., penicillin-resistant *S. pneumoniae*, MRSA) and the recent use of prophylactic or therapeutic antibiotics should be considered when initiating empiric therapy. When the organism is identified, antibiotic susceptibility testing should be performed, and subsequent therapy based on the results of susceptibility testing **(AIII)**.

HIV-infected children whose immune systems are not seriously compromised (CDC Immunologic Category I)[76] and who are not neutropenic can be expected to respond similarly to HIV-uninfected children and should be treated for the most likely bacterial organisms **(AIII)**. Based only on expert opinion, mild to moderate community-acquired pneumonia in HIV-infected children with only mild or no immunosuppression who are fully immunized (especially against *S. pneumoniae* and Hib) and who are receiving effective cART can be treated with oral antibiotics (usually oral amoxicillin), according to the same guidelines as for healthy children **(BIII)**.[76] However, many experts have a lower threshold for hospitalizing these children to initiate treatment. In addition, broader-spectrum antimicrobial agents for initial empiric therapy are sometimes chosen because of the potentially higher risk of non-susceptible pneumococcal infections in HIV-infected children.[17,22,24,25] Thus, options for empiric therapy for HIV-infected children outside of the neonatal period who are hospitalized for suspected community-acquired bacteremia or bacterial pneumonia include ampicillin or an extended-spectrum cephalosporin (e.g, ceftriaxone, cefotaxime) **(AIII)**.[8,77,78] The addition of vancomycin or other antibiotic for suspected bacterial meningitis should follow the same guidelines as for HIV-uninfected children.[79] The addition of azithromycin or other macrolide can be considered for hospitalized patients with pneumonia to treat other common community-acquired pneumonia pathogens (*M. pneumoniae*, *C. pneumoniae*). If MRSA is suspected or the prevalence of MRSA is high (i.e., >10%) in the community, clindamycin (for non-CNS infections), doxycycline (non-CNS, for childen aged >8 years) or vancomycin can be added (choice based on local susceptibility patterns).[80-82] Neutropenic children also should be treated with an appropriate antipseudomonal drug with consideration for adding an aminoglycoside if infection with *Pseudomonas* spp. is likely. Severely immunocompromised HIV-infected children with invasive or recurrent bacterial infections require expanded empiric antimicrobial treatment covering a broad range of resistant organisms similar to that chosen for suspected catheter sepsis pending results of diagnostic evaluations and cultures **(AIII)**.

Initial empiric therapy for HIV-infected children with suspected intravascular catheter sepsis should target both gram-positive and enteric gram-negative organisms, with combinations that include agents with anti-*Pseudomonas* activity and vancomycin, which is active against MRSA **(AIII)**. Factors such as response to therapy, clinical status, identification of pathogen, and need for ongoing vascular access will determine the need for and timing of catheter removal.

### *Monitoring and Adverse Events (Including IRIS)*

The response to appropriate antibiotic therapy should be similar in HIV-infected and HIV-uninfected children, with a clinical response usually observed within 2 to 3 days after initiation of appropriate antibiotics, recognizing that radiologic improvement in patients with pneumonia may lag behind clinical response. Whereas HIV-infected adults experience high rates of adverse and even treatment-limiting reactions to TMP–SMX, in HIV-infected children, serious adverse reactions to TMP–SMX appear to be much less of a problem.[84]

Immune reconstitution inflammatory syndrome (IRIS) has not clearly been described in association with treatment of bacterial infections in children. Reports of pneumonia, abscess and other bacterial infection in children during the first several weeks of effective cART have been attributed to IRIS[85,86] but are more likely related to persistent immune suppression. Suspicion of IRIS in a child being treated for a bacterial infection should raise concern for the presence of a different or additional infection or for inadequately treated infection mimicking IRIS.

### *Preventing Recurrence*

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

TMP-SMX (administered daily for PCP prophylaxis) and azithromycin or atovaquone-azithromycin (administered for MAC prophylaxis) also may reduce the incidence of serious bacterial infections in children with recurrent serious bacterial infections. Administration of antibiotic chemoprophylaxis to HIV-infected children who have frequent recurrences of serious bacterial infections despite cART (e.g., >2 serious bacterial infections in a 1-year period despite cART) can be considered **(CIII)**; however, caution is required when using antibiotics solely to prevent recurrence of serious bacterial infections because of the potential for development of drug-resistant microorganisms and drug toxicity. In rare situations in which cART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis **(CI)**.[15]

### *Discontinuing Secondary Prophylaxis*

PACTG 1008 demonstrated that discontinuing MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved sustained (i.e., ≥16 weeks) immune reconstitution (CD4 percentage >20% to 25%) while receiving cART did not result in excessive rates of serious bacterial infections.[6] Antibiotics for secondary prophylaxis of serious bacterial infections should be discontinued in HIV-infected children who have achieved sustained (i.e., ≥3 months) immune reconstitution (CD4 percentage ≥25% if ≤6 years old; CD4 percentage ≥20% or >350 cells/mm$^3$ if >6 years old) **(BII)**.

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## Dosing Recommendations for Prevention and Treatment of Invasive Bacterial Infections

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis**<br>*S. pneumoniae* and other invasive bacteria | • Pneumococcal, meningococcal, and Hib vaccines<br>• IVIG 400 mg/kg body weight every 2–4 weeks | • TMP-SMX 75/375 mg/$m^2$ body surface area per dose by mouth twice daily | See Figures 1 and 2 for detailed vaccines recommendations.<br>Vaccines Routinely Recommended for Primary Prophylaxis. Additional Primary Prophylaxis Indicated For:<br>• Hypogammaglobulinemia (that is, IgG <400 mg/dL)<br>Criteria for Discontinuing Primary Prophylaxis:<br>• Resolution of hypogammaglobulinemia<br>Criteria for Restarting Primary Prophylaxis:<br>• Relapse of hypogammaglobulinemia |
| **Secondary Prophylaxis**<br>*S. pneumoniae* and other invasive bacteria | • TMP-SMX 75/375 mg/$m^2$ body surface area per dose by mouth twice daily | • IVIG 400 mg/kg body weight every 2–4 weeks | Secondary Prophylaxis Indicated:<br>• >2 serious bacterial infections in a 1-year period in children who are unable to take cART<br>Criteria for Discontinuing Secondary Prophylaxis:<br>• Sustained (≥ 3 months) immune reconstitution (CD4 percentage ≥25% if ≤6 years old; CD4 percentage ≥20% or CD4 count >350 cells/$mm^3$ if >6 years old)<br>Criteria For Restarting Secondary Prophylaxis:<br>• >2 serious bacterial infections in a 1-year period despite cART |
| **Treatment**<br>Bacterial pneumonia; *S. pneumoniae*; occasionally *S. aureus*, *H. influenzae*, *P. aeruginosa* | • Ceftriaxone 50–100 mg/kg body weight per dose once daily, or 25–50 mg/kg body weight per dose twice daily IV or IM (max 4 g/day), or<br>• Cefotaxime 40–50 mg/kg body weight per dose 4 times daily, or 50–65 mg/kg body weight 3 times daily (max 8–10 g/day) IV | • Cefuroxime, 35–50 mg/kg body weight per dose 3 times daily (max 4–6 g/day) IV | For children who are receiving effective cART, have mild or no immunosuppression, and have mild to moderate community-acquired pneumonia, oral therapy option would be amoxicillin 45 mg/kg body weight per dose twice daily (maximum dose: 4 g per day).<br>Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (*M. pneumoniae*, *C. pneumoniae*).<br>Add clindamycin or vancomycin if methicillin-resistant *S. aureus* is suspected (base the choice on local susceptibility patterns).<br>For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (such as ceftazidime or cefepime instead of ceftriaxone).<br>Consider PCP in patients with severe pneumonia or more advanced HIV disease.<br>Evaluate for tuberculosis, cryptococcosis, and endemic fungi as epidemiology suggests. |

**Key to Acronyms:** cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; IgG = immunoglobulin G; IM = intramuscular; IV = intravenous; IVIG = intravenous immune globulin; LIP = lymphocytic interstitial pneumonia; PCP = *Pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole

# *Candida* Infections (Last updated January 23, 2020; last reviewed January 31, 2019)

**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**).

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Rating System

*Strength of Recommendation:* Strong; Weak

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

## Epidemiology

The most common fungal infections in children with HIV infection are caused by *Candida* spp. Candidiasis is characterized as either localized or invasive. Localized disease caused by *Candida* is characterized by limited tissue invasion of the skin or mucosa. Examples of localized candidiasis include oropharyngeal and esophageal disease, vulvovaginitis, and diaper dermatitis. *Candida* can gain access to the bloodstream causing candidemia either by penetration from local mucosal or cutaneous infection or via medical devices such as central venous catheters. Once candidemia is present, widespread hematogenous dissemination to any organ is possible. Concerning manifestations of disseminated infection include, but are not limited to, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease. Candidemia with or without dissemination is collectively referred to as invasive candidiasis.

### *Localized Candidiasis*

Oral thrush and diaper dermatitis occur in 50% to 85% of children with HIV infection. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent opportunistic infections in children with HIV infection during the combination antiretroviral therapy (cART) era (28% of children), with an incidence rate of 0.93 per 100 child-years. The incidence of esophageal or tracheobronchial candidiasis has decreased from 1.2

per 100 child-years before the pre-cART era to 0.08 per 100 child-years during the cART era (2001–2004).[1] However, *Candida* esophagitis continues to be seen in children who are not responding to antiretroviral therapy (ART).[2,3] Children who develop esophageal candidiasis despite ART may be less likely to have typical symptoms (e.g., odynophagia, retrosternal pain) or have concomitant OPC;[4] during the pre-cART era, concomitant OPC occurred in 94% of children with *Candida* esophagitis.[2] Risk factors for esophageal candidiasis include low CD4 T lymphocyte (CD4) cell count (<100 cells/mm$^3$), high viral load (>5,000 copies/mL), and neutropenia (absolute neutrophil count [ANC] <500 cells/mm$^3$).[1-3,5]

### *Invasive Candidiasis*

Invasive candidiasis is less frequent than localized disease in children with HIV infection. However, *Candida* can disseminate from the esophagus, particularly during co-infection with herpes simplex virus (HSV) or cytomegalovirus (CMV).[2,6] Candidemia occurs in up to 12% of children with HIV infection who have chronic indwelling central venous catheters placed for administration of total parenteral nutrition or intravenous (IV) antibiotics.[3,7] While *Candida albicans* remains the most common cause of all candidiasis, approximately 50% of reported cases of *Candida* bloodstream infections in children are caused by non-*albicans Candida* spp. including: *Candida tropicalis*, *Candida kefyr* (*Candida pseudotropicalis*), *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dubliniensis*. In some settings, non-albicans species cause the majority of blood stream infections. The non-*albicans Candida* species are important to identify because several are resistant to antifungals. In general, *C. krusei* is considered resistant to fluconazole, and *C. glabrata* isolates have an increased rate of resistance to both fluconazole and voriconazole. Recently, an increasing number of *C. glabrata* isolates are also resistant to echinocandins. *C. lusitaniae* is inherently resistant to amphotericin B. Many children who develop candidemia have previously received systemically absorbed oral antifungal azole compounds (e.g., ketoconazole, fluconazole) for control of oral and esophageal candidiasis, which may predispose to resistant isolates.[3] In one study of Cambodian children with HIV infection and on ART who had candidiasis, seven (75%) of nine isolated *C. glabrata* were resistant to fluconazole, and three (40%) of seven *C. parapsilosis* isolated were resistant to >3 azole agents.[8] However, clinicians should be aware of local resistance trends as the epidemiology of species-specific resistance may vary widely by geographic location and hospital.

## Clinical Manifestations

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

Esophageal candidiasis often presents with odynophagia, dysphagia, or retrosternal pain, and children, unlike adults, often experience nausea and vomiting. Therefore, children with esophageal candidiasis may present with dehydration and weight loss. Classic symptoms and signs of OPC may be absent in children with esophageal candidiasis, particularly those receiving ART.

New-onset fever in a child with HIV infection who has advanced disease, a central venous catheter, or both is the most common clinical manifestation of candidemia. Unfortunately, there are limited clinical signs or symptoms to denote dissemination to a particular organ, and detection of end organ involvement is often dependent on radiographic imaging. For example, renal candidiasis can present with candiduria, but ultrasonographic demonstration of renal parenchymal lesions is often not associated with symptoms related to renal disease.[3]

## Diagnosis

Oral candidiasis can be diagnosed with a potassium hydroxide preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. Esophageal candidiasis has a classic cobblestone appearance on barium swallow. Findings on endoscopy may range from a few, small, raised, white plaques to elevated confluent plaques with hyperemia and extensive ulceration. Endoscopy is also helpful for ruling out other causes of refractory esophagitis, such as HSV, CMV, and *Mycobacterium avium* complex.

Candidemia is best diagnosed with blood cultures using lysis-centrifugation techniques.[3] or automated broth-based systems.[9] When candidemia is present, retinal examination for endophthalmitis, cardiac echocardiogram for endocarditis, abdominal computed tomography or ultrasound for hepatic or renal involvement, and bone scans for osteomyelitis (if suspected by symptoms) should be considered.

New diagnostic techniques such as the urine D-arabinitol/L-arabinitol ratio,[10,11] serum D-arabinitol/creatinine ratio,[12,13] *Candida* mannan antigen and anti-mannan antibody,[14,15] (1,3)-beta-D-glucan assay,[16,17] T2 biosystems for *Candida*[18] and real-time polymerase chain reaction[19,20] are promising diagnostic alternatives under development for early diagnosis of invasive candidiasis. Although several of these assays are helpful in diagnosing invasive candidiasis in adult patients, none of them have been validated or Food and Drug Administration (FDA)-approved for use in children.

As noted above, candidemia can result in dissemination of infection to any organ site. There are no pediatric data to guide decisions on when to perform additional diagnostic testing to evaluate for a deep-seated focus. However, among children with persistent candidemia, further investigation for dissemination should strongly be considered. Additional diagnostics to consider in this clinical scenario would include, but not be limited to, an echocardiogram, abdominal ultrasound to evaluate the kidney, liver and spleen, a lumbar puncture and an eye exam **(strong, low)**.

## Prevention Recommendations

### *Preventing Exposure*

*Candida* organisms are common commensals on mucosal surfaces in healthy individuals; no measures are available to reduce exposure to these fungi except by reducing exposure to unneeded antibiotics that may predispose a patient to *Candida* colonization.

### *Preventing First Episode of Disease*

Routine primary prophylaxis of candidiasis in infants and children with HIV infection is not indicated for multiple reasons. In the era of ART, the prevalence of serious *Candida* infections (e.g., esophageal or invasive candidiasis) is low. Additionally, there is a lack of randomized controlled trials of routine, primary prophylaxis of candidiasis in children with HIV infection, concern for potentiating resistant *Candida* strains, and the potential for drug-drug interactions between antifungal and antiretroviral (ARV) agents.[21]

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

#### Oropharyngeal Candidiasis

Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral nystatin suspension for 7 to 14 days **(strong, high)**.[22-25] Debridement can be considered as adjunctive therapy in OPC. Resistance to clotrimazole can develop because of previous exposure to clotrimazole or to other azole drugs; resistance correlates with refractory mucosal candidiasis.[26]

Systemic therapy with 1 of the oral azoles (e.g., fluconazole, itraconazole, posaconazole) for 7 to 14 days is recommended for moderate to severe OPC.[22-24] Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants, easier to administer to children than the topical therapies, and the recommended treatment when systemic therapy is used **(strong, high)**.[23,27]

For fluconazole-refractory OPC, itraconazole oral solution should be used. Itraconazole solution has efficacy comparable to fluconazole and can be used to treat OPC, although it is less well tolerated than fluconazole **(weak, low)**.[28] Gastric acid enhances absorption of itraconazole solution, thus it should be taken without food when possible. Itraconazole capsules and oral solution should not be used interchangeably because, at the same dose, drug exposure is greater with the oral solution than with capsules, and absorption of the capsule formulation varies. Ketoconazole tablet absorption also varies, and therefore neither itraconazole capsules nor ketoconazole tablets are recommended for treating OPC if fluconazole or itraconazole solutions are available **(strong, moderate)**. Additional choices for fluconazole-refractory OPC include voriconazole or posaconazole, or IV treatment with amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin), if required.

### Esophageal Disease

Systemic therapy is essential for esophageal disease **(strong, high)** and should be initiated empirically in children with HIV infection who have OPC and esophageal symptoms. In most patients, symptoms should resolve within days after the start of effective therapy. Oral fluconazole for 14 to 21 days is highly effective for treatment of *Candida* esophagitis and is considered first line therapy **(strong. high)**.[22,29] IV fluconazole, amphotericin B, or an echinocandin should be used for patients who cannot tolerate oral therapy. For fluconazole-refractory disease, itraconazole solution, posaconazole, voriconazole, amphotericin B, or an echinocandin are alternatives.

### Invasive Candidiasis

The treatment of choice for invasive disease in children with HIV infection depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). An echinocandin is recommended for severely ill children with candidiasis because of the fungicidal nature of these agents, as well as the lack of adverse events **(strong, high)**. Fluconazole is a reasonable alternative for patients who are less critically ill and who have no recent azole exposure. Voriconazole can be used in situations in which mold coverage is also warranted. For infections with *C. glabrata*, an echinocandin is recommended because of the increasing resistance seen against fluconazole for this species **(strong, moderate)**. Despite this recommendation, clinicians should be aware of the increasing frequency of *C. glabrata* echinocandin resistance. For patients already receiving fluconazole or voriconazole who are clinically improving despite *C. glabrata* infection, continuing use of the azole is reasonable. Infection with *C. krusei* should be treated with an echinocandin because of the inherent resistance to fluconazole. For infection with *C. parapsilosis*, fluconazole or amphotericin B is recommended **(strong, moderate)**. Previous data suggested a decreased response of *C. parapsilosis* isolates to echinocandins.[30] However, recent adult comparative effectiveness data reveal that initial therapy with an echinocandin for *C. parapsilosis* did not result in worse outcomes.[31] Thus, if a patient is receiving empiric therapy with an echinocandin and showing clinical improvement when culture of *C. parapsilosis* returns, continuing with this therapy is reasonable.

For many of these clinical scenarios, amphotericin B is an effective but less attractive alternative given concerns for therapy-related toxicity **(weak, moderate)**. Amphotericin B lipid formulations may be preferable to conventional amphotericin B deoxycholate given their improved side effect profile (see Monitoring and Adverse Events section below), especially in children at high risk of nephrotoxicity due to preexisting renal disease or use of other nephrotoxic drugs **(weak, moderate)**. Regardless of the antifungal agent chosen, the recommended duration of therapy for candidemia is 14 days after documented clearance from the blood along with resolution of neutropenia (if initially present) and resolution of clinical signs and symptoms of candidemia. In children with evidence of deep-seated foci (e.g., endocarditis or osteomyelitis), duration of therapy will be longer and ultimately should be guided by an infectious diseases specialist.

If a child is initiated on an intravenous antifungal agent, such as an echinocandin or an amphotericin B formulation, step-down therapy to an oral agent such as fluconazole when the patient is clinically improved to complete the course can be considered **(strong, moderate)**. Species identification is preferred when stepping down to fluconazole because of intrinsic or acquired drug resistance among certain *Candida* spp. (e.g., *C. krusei*, *C. glabrata*).

Finally, in children with HIV infection who have a central venous catheter in place at the time of candidemia onset, the central line should always be removed when feasible **(strong, moderate)**.[3,32] While there has never been a randomized controlled trial performed that proves the benefit of removal of a central venous catheter, there are well-designed observational studies that have reasonably accounted for confounding by indication for line removal (i.e., central lines were removed in the relatively well patients and retained in the critically ill patient) and still show a benefit for line removal. Additionally, Andes et al. performed a patient level systemic review of adult patients with candidemia and found that central line removal provided a protective effect against mortality. Therefore, it is reasonable to conclude that a central venous catheter should be removed when feasible.

## Pharmacokinetics and Dosing of Antifungal Agents

### *Azoles*

Fluconazole pharmacokinetics (PK) vary significantly with patient age, and fluconazole is rapidly cleared in children.

Daily fluconazole dosing for invasive candidiasis requires higher doses of fluconazole (12 mg/kg/day) than are used for mucocutaneous disease (6 mg/kg/day), with many experts suggesting a loading dose of fluconazole 25 mg/kg for children.

Because of more rapid clearance in children, fluconazole administered to children at 12 mg/kg/day provides exposure similar to standard 400-mg daily dosing in adults. Dosing of fluconazole for invasive candidiasis in children and adolescents should generally not exceed 600 mg/day.[33]

The bioavailability of itraconazole oral solution is lower in children than in adults; therefore, dosing in children should be 2.5 to 5 mg/kg per dose twice daily **(strong, moderate)**. This dosing contrasts with the once daily dosing of itraconazole used in adult patients. Administrating itraconazole oral solution on an empty stomach improves absorption (in contrast to the capsule formulation, which is best administered under fed conditions), and monitoring itraconazole serum concentrations, like most azole antifungals, is key in management (generally itraconazole trough levels should be >0.5 to 1 µg/mL; trough levels >3 µg/mL may be associated with increased toxicity). In adult patients, itraconazole is recommended to be loaded at 200 mg twice daily for 2 days, followed by itraconazole 200 mg daily starting on the third day.

There is now considerable experience with voriconazole in children, including for treatment of esophageal candidiasis and candidemia.[2,22,34,35] Usually children are started on voriconazole IV and then switched to oral administration to complete therapy after they are clinically stable. The optimal dose of voriconazole used in children is higher than that used in adults because of differing PK. Voriconazole has been shown to be tolerated to a similar degree regardless of dosage and age; a maintenance daily dosage of 8 mg/kg IV in children aged 2 to 11 years was needed to attain voriconazole plasma levels achieved in adults with a 4 mg/kg IV dosage. Also, the oral bioavailability of voriconazole in children is lower than in adults (approximately 50%), therefore, in children, weight-adjusted dosages are higher for oral therapy than for IV therapy.[34,35] The recommended voriconazole dosage for children is 9 mg/kg every 12 hours IV loading on day 1, followed by voriconazole 8 mg/kg IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg orally every 12 hours **(strong, moderate)**.[36] In addition, therapeutic trough voriconazole drug levels (generally thought to be >1 to 2 µg/mL) should be monitored because of significant interpatient variability in voriconazole PK in children with invasive fungal infection.[37] For example, voriconazole clearance depends on allelic polymorphisms of CYP2C19, resulting in poor and extensive metabolizers of voriconazole.[38,39] It is estimated that 15% to 20% of Asian and 3% to 5% of white and African populations are poor metabolizers of voriconazole, further underscoring the importance of monitoring voriconazole levels to ensure proper dosing.[38]

There is limited experience with the use of **posaconazole** in children and currently has an oral suspension and extended-release tablet formulation approved for patients 13 years and older, and an IV formulation approved for patients aged ≥18 years. Effective absorption of the oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The tablet formulation has better absorption given its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient is unable to take food, the tablet is recommended. There is potential for overdosing if this tablet formulation is dosed inappropriately.[40] The exact pediatric dosing for posaconazole has not been completely determined and the dose recommended by some experts for treating invasive disease is posaconazole 18 mg/kg/day divided three times daily. The pediatric IV or extended release tablet dosing is completely unknown and under study, but adolescents can likely follow the adult dosing schemes. In adult patients, IV posaconazole is loaded at 300 mg twice daily on the first day, then posaconazole 300 mg once daily starting on the second day. Similarly, in adult patients the extended-release tablet is dosed as posaconazole 300 mg twice daily on the first day, then 300 mg once daily starting on the second day. In adult patients, the maximum amount of posaconazole oral suspension given is 800 mg per day (given its excretion), and that dosage has been given as posaconazole 400 mg twice daily or 200 mg four times a day in severely ill patients because of findings of a marginal increase in exposure with more frequent dosing.

Isavuconazole is a new triazole that was FDA-approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis with both oral (capsules only) and IV formulations. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to isavuconazonium sulfate 372 mg) every 8 hours for 2 days (6 doses), followed by isavuconazole 200 mg once daily for maintenance dosing. No specific pediatric dosing data currently exist for isavuconazole.

*Echinocandins*

Data from studies using echinocandins (caspofungin, micafungin, and anidulafungin) are now sufficient to recommend these agents as alternatives to fluconazole for esophageal candidiasis, and as first-line therapy for invasive candidiasis **(strong, high)**.[41-55] However, echinocandins are not recommended for treatment of central nervous system *Candida* infections due to concerns that these agents penetrate cerebrospinal fluid poorly.

A PK study of caspofungin in immunocompromised children with HIV infection aged 2 to 17 years demonstrated that 50 mg/m$^2$ body surface area/day (70 mg/day maximum) provides exposure comparable to that obtained in adults receiving a standard 50-mg daily regimen.[43] Significantly higher doses of caspofungin have been studied in adult patients without any clear added benefit in efficacy, but if the 50 mg/m$^2$ dose is tolerated and does not provide adequate clinical response, the daily dose can be increased to 70 mg/m$^2$. Dosing for caspofungin in neonates is 25 mg/m$^2$/day.

The recommended dose of micafungin for children aged 2 years to 17 years is 2 to 4 mg/kg daily, but neonates require doses of micafungin 10 mg/kg daily **(strong, moderate)**.[47-51] Micafungin demonstrates dose-proportional PK, and an inverse relationship between age and clearance, suggesting a need for increased dosage in young children.[52] Clearance of the drug in neonates was more than double that in older children and adults.[53] Dosages of micafungin 10 mg/kg/day are recommended in premature neonates, resulting in area-under-the-curve values consistent with an adult dosage of micafungin 100 to 150 mg/day.

One PK study of anidulafungin in 25 neutropenic children without HIV infection aged 2 years to 17 years (including 12 children aged 2 years to 11 years and 13 children aged 12 years to 17 years) showed drug concentrations with 0.75 mg/kg per dose and 1.5 mg/kg per dose were similar to drug concentrations in adults with 50 mg per dose and 100 mg per dose, respectively.[54] In a case report of a term 11-day infant with peritoneal candidiasis and failure of (liposomal amphotericin B [L-AmB]) therapy, an IV dose of 1.5 mg/kg/day of anidulafungin was successful in treating the infection.[55]

*Polyenes*

Conventional amphotericin B (sodium deoxycholate complex) PK in children and adults are very similar. In children who have azotemia or hyperkalemia, or who are receiving high doses of amphotericin B (i.e., ≥1 mg/kg), a longer infusion time of 3 to 6 hours is recommended **(weak, moderate)**.[56] Three lipid preparations of amphotericin B approved in the mid-1990s decrease toxicity with no apparent decrease in clinical efficacy. Decisions on which lipid amphotericin B preparation to use should, therefore, largely focus on side effects and costs. Two clinically useful lipid formulations exist: one in which ribbon-like lipid complexes of amphotericin B are created (amphotericin B lipid complex [ABLC]), Abelcet, and one in which amphotericin B is incorporated into true liposomes (L-AmB), AmBisome. The standard dosage of these preparations is 5 mg/kg/day, in contrast to the 1 mg/kg/day of amphotericin B-D. In most studies, the side effects of L-AmB were somewhat less than those of ABLC, but both have significantly fewer side effects than AmB-D. The advantage of the lipid preparations is the ability to safely deliver a greater overall dose of the parent AmB drug. Despite *in vitro* concentration-dependent killing, a clinical trial comparing L-AmB at doses of 3 mg/kg/day and 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity.[57] Therefore, use of any AmB preparations at very high dosages (i.e., >5 mg/kg/day) is generally not recommended, as it will likely only incur greater toxicity with no real therapeutic advantage. There are reports of using higher dosing in very difficult infections where amphotericin B is the first-line therapy (e.g., mucormycosis), and while experts remain divided on this practice, it is clear that ≥5 mg/kg/day of a lipid amphotericin B formulation should be used. Amphotericin B has a long terminal half-life and, coupled with the concentration-dependent killing, the agent is best used as single daily doses. These PK explain the use in some studies of once weekly amphotericin B for antifungal prophylaxis. If the overall amphotericin B exposure needs to be decreased due to toxicity, it is best to increase the dosing interval (e.g., 3 times weekly) but retain the full mg/kg dose for optimal PK.

*Combination antifungal therapy*

Data in adults are limited on use of combination antifungal therapy for invasive candidal infections; combination amphotericin B and fluconazole resulted in more rapid clearance of *Candida* from the bloodstream but no difference in mortality.[22] Flucytosine has been used in combination with amphotericin B in some children with severe invasive candidiasis, particularly in those with central nervous system disease, but it has a narrow therapeutic index. Overall there are insufficient data to support routine use of combination therapy in children with invasive candidiasis **(weak, low)**.[58]

## *Monitoring and Adverse Events, Including IRIS*

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

The azole drugs have relatively low rates of toxicity, but because of their ability to inhibit the cytochrome P450 (CYP450)-dependent hepatic enzymes (ketoconazole has the strongest inhibitory effect) and their metabolism by these enzymes, they can interact substantially with other drugs undergoing hepatic metabolism. These interactions can result in decreased plasma concentration of the azole because of increased metabolism induced by the coadministered drug, or development of unexpected toxicity from the coadministered drug because of increased plasma concentrations secondary to azole-induced alterations in hepatic metabolism. The potential for drug interactions, particularly with ARV drugs such as protease inhibitors, should be carefully evaluated before initiation of therapy **(strong, low)**.

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting

(10% to 40% of patients). Skin rash and pruritus can occur with all azoles; rare cases of Stevens-Johnson syndrome and alopecia have been reported with fluconazole therapy. All azole drugs are associated with asymptomatic increases in transaminases (1% to 13% of patients). Hematologic abnormalities have been reported with itraconazole, including thrombocytopenia and leukopenia. Of the azoles, ketoconazole is associated with the highest frequency of side effects. Its use has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia, hemolytic anemia, and transaminitis. Dose-related, reversible visual changes, such as photophobia and blurry vision, have been reported in approximately 30% of patients receiving voriconazole.[59] Cardiac arrhythmias and renal abnormalities, including nephritis and acute tubular necrosis, also have been reported with voriconazole use. Hallucinations have also been attributed to voriconazole exposure.[60] More recently, voriconazole administration has been associated with fluorosis. Voriconazole is a tri-fluorinated agent with up to 16% fluoride and after prolonged exposure can result in excess fluoride accumulation in the recipient. Patients will often present with non-specific bone pain and have periosteal reaction seen on radiographs.[61] Another common reason for discontinuation of voriconazole is phototoxic skin reaction associated with chronic use; these phototoxic skin reactions have been reported to develop into carcinoma.[62,63]

Amphotericin B deoxycholate undergoes renal excretion as inactive drug. Adverse effects of amphotericin B are primarily nephrotoxicity, defined by substantial azotemia from glomerular damage, and can be accompanied by hypokalemia from tubular damage. Nephrotoxicity is exacerbated by use of concomitant nephrotoxic drugs. Permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration before amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting occur less frequently in children than in adults. Onset of the febrile reactions occurs usually within 1 to 3 hours after the infusion is started; the reactions typically last for <1 hour and tend to decrease in frequency over time. Pre-treatment with acetaminophen or diphenhydramine may alleviate febrile reactions. Idiosyncratic reactions, such as hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur.

Lipid formulations of amphotericin B cause less acute and chronic toxicity than amphotericin B deoxycholate. In approximately 20% of children, lipid formulations of amphotericin B can cause acute, infusion-related reactions, including chest pain; dyspnea; hypoxia; severe pain in the abdomen, flank, or leg; or flushing and urticaria. Compared with infusion reactions with conventional amphotericin B, most (85%) of the reactions to the lipid formulations occur within the first 5 minutes after infusion and rapidly resolve with temporary interruption of the amphotericin B infusion and administration of IV diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

The echinocandins have an excellent safety profile, presumably because the antifungal target (β-1,3-glucan) is lacking in humans. In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated, although 3 patients had adverse events potentially related to the drug (hypokalemia in all 3 children, elevated bilirubin in 2 children, and decreased hemoglobin and elevated alanine aminotransferase in 1 child).[43] In this study, children weighing <50 kg received caspofungin 0.8 to 1.6 mg/kg body weight daily, and those weighing >50 kg received the adult dosage. In the PK study of 39 children who received caspofungin at 50 mg/m$^2$ body surface area/day, five (13%) patients experienced one or more drug-related clinical adverse events, including 1 patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. One or more drug-related laboratory adverse events were reported in 2 patients, including one patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related adverse events in this study were considered serious or led to discontinuation of caspofungin.[43] In a prospective multicenter trial for primary or salvage treatment of *Candida* and *Aspergillus* infections in 48 children aged 6 months to 17 years, a caspofungin dose of 50 mg/m$^2$ per day (maximum: 70 mg/day; after 70 mg/m$^2$ on day 1) was generally well tolerated, with drug-related clinical and laboratory adverse events occurring in 26.5% and 34.7% of patients, respectively, similar to rates seen in adults. Drug-related clinical adverse events were typically mild and did not lead to therapy discontinuation. An increased level of hepatic transaminase, often occurring in the context of other medical conditions or concomitant therapies that may have contributed to elevations in hepatic enzymes, represented the most common drug-related laboratory adverse event. None of the drug-related laboratory adverse events led to therapy interruption or discontinuation.[45]

In a double-blind randomized trial comparing micafungin with L-amB in 48 children aged <16 years with clinical signs of systemic *Candida* infection or culture confirmation of *Candida* infection, a micafungin daily dose of 2 mg/kg of body weight for patients who weighed 40 kg, and 100 mg for patients who weighed >40 kg, was well tolerated. Adverse events were similar for both treatment arms and reflected those experienced by patients with comorbid conditions. These adverse events included sepsis, fever, vomiting, diarrhea, anemia, thrombocytopenia, and hypokalemia. Patients in the micafungin group experienced significantly fewer adverse events leading to treatment discontinuation than those in the amphotericin B group (2/25 [3.8%] vs. 9/54 [16.7%], respectively), suggesting a safety advantage for micafungin in this population. Two patients receiving micafungin experienced serious adverse events, including a worsening of renal failure, a preexisting condition, and a moderate increase in serum creatinine resulting in discontinuation of therapy. Patients rarely experienced clinically meaningful changes in creatinine, aspartate transaminase, alanine transaminase, or bilirubin during treatment. Children aged ≥2 years in the micafungin treatment arm experienced a smaller mean peak decrease in the estimated glomerular filtration rate than those in the L-amB arm.[48]

A multicenter, ascending-dosage study of anidulafungin in 25 children with neutropenia, without HIV infection and aged 2 years to 17 years, showed anidulafungin to be well tolerated and observed no drug-related serious adverse events. Fever was observed in one patient with a National Cancer Institute toxicity grade of 3, and facial erythema was observed in another patient, which resolved after the infusion rate was decreased.[54]

Immune reconstitution inflammatory syndrome (IRIS) associated with *Candida* infection has not been described in children with HIV infection. However, evidence suggests that candidiasis (other than *Candida* esophagitis) occurs with increased frequency in adults during the first 2 months after initiation of ART.[64]

## *Managing Treatment Failure*

### Oropharyngeal and Esophageal Candidiasis

If OPC initially is treated topically, failure or relapse should be treated with oral fluconazole or itraconazole oral solution **(strong, high)**.[28,65]

Approximately 50% to 60% of patients with fluconazole-refractory OPC and 80% of patients with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution **(weak, moderate)**.[66,67] Posaconazole is a second-generation orally bioavailable triazole that has been effective in adults with HIV infection who have azole-refractory OPC or esophageal candidiasis.[68] However, experience in children is limited, and an appropriate dosage for children aged <13 years has not been defined; thus data in children are insufficient to recommend its use in children with HIV infection **(weak, low)**.[69,70]

An Amphotericin B dose of 1 mL given orally four times daily of a 100-mg/mL suspension sometimes has been effective in patients with OPC who do not respond to itraconazole solution; however, this product is not available in the United States **(weak, low)**.[67] Low-dose IV amphotericin B (0.3–0.5 mg/kg/day) has been effective in children with refractory OPC or esophageal candidiasis **(strong, moderate)**.[22,67,71,72]

Data on the use of echinocandins to treat azole-refractory OPC or esophageal candidiasis in children with and without HIV infection are limited; however, given their excellent safety profile, the echinocandins[69] could be considered for treatment of azole-refractory esophageal candidiasis **(weak, moderate)**.

### Invasive Disease

As noted above, the treatment of choice for invasive disease in children with HIV infection depends on severity of disease, previous azole exposure, and *Candida* isolate and antifungal susceptibility (if known).

An echinocandin is recommended for severely ill children and fluconazole is recommended as a first line alternative for children who are not critically ill and have no recent azole exposure. The role of the echinocandins in invasive candidiasis has not been well studied in children with HIV infection, however there is extensive clinical experience with echinocandins in children. Invasive candidiasis associated with neutropenia in patients undergoing bone marrow transplantation has been treated successfully with this class of antifungals. These agents should be considered as first-line treatment of invasive candidiasis in neutropenic or critically-ill children **(strong, moderate)**.

Various amphotericin B formulations exist for management of refractory disease. Although lipid amphotericin B formulations appear to be at least as effective as conventional amphotericin B for treating serious fungal infections,[73,74] the drugs are considerably more expensive than conventional amphotericin B. However, the lipid formulations have less acute and chronic toxicity. Two lipid formulations are used: amphotericin B lipid complex and liposomal amphotericin B lipid complex.[75-77]

For invasive candidiasis, amphotericin B lipid complex is administered as 5 mg/kg body weight IV once daily over 2 hours.[75,76,78] Liposomal amphotericin B is administered IV as 3 to 5 mg/kg body weight once daily over 1 to 2 hours.

### *Preventing Recurrence*

Similar to recommendations regarding primary prophylaxis, secondary prophylaxis of recurrent OPC is also not routinely recommended because treatment of recurrence is typically effective, there are concerns for drug-drug interactions, the potential exists for development of resistance, and prophylaxis can prove costly **(strong, moderate)**. Immune reconstitution with ART in immunocompromised children should be a priority **(strong, weak)**. However, when recurrences are frequent and severe, secondary prophylaxis may be considered on a case-by-case scenario. Data from studies of adults with HIV infection on ART suggest that suppressive therapy with systemic azoles, either with oral fluconazole **(weak, moderate)** or voriconazole or itraconazole solution **(weak, moderate)**, can be effective.[28,79-81]

Experience with adults with HIV infection suggests that, in patients with initial fluconazole-refractory OPC or esophageal candidiasis that subsequently responded to voriconazole, posaconazole or echinocandins, continuation of the effective drug as secondary prophylaxis until ART produces immune reconstitution can be effective **(weak, low)**.

### *Discontinuing Secondary Prophylaxis*

In situations when secondary prophylaxis is instituted, no data exist on which to base a recommendation regarding discontinuation. On the basis of experience in adults with HIV infection with other opportunistic infections, discontinuation of secondary prophylaxis can be considered when a patient's CD4 count or percentage has risen to CDC Immunologic Category 2 or 1 **(weak, low)**.[82]

## Recommendations

### *Treatment*

**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)**.

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## **Dosing Recommendations for Prevention and Treatment of Candidiasis** (page 1 of 3)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Prophylaxis | Not routinely recommended | N/A | N/A |
| Secondary Prophylaxis | Not routinely recommended but can be considered for frequent severe recurrences.<br><br><u>Fluconazole</u>:<br>• Fluconazole 3–6 mg/kg body weight daily (maximum 200 mg) by mouth, or itraconazole oral solution, 2.5 mg/kg body weight/dose twice daily | N/A | <u>Secondary Prophylaxis Indicated</u>:<br>• Frequent or severe recurrences<br><br><u>Criteria for Discontinuing Secondary Prophylaxis</u>:<br>• When CD4 count or percentage has risen to CDC immunologic Category 2 or 1<br><br><u>Criteria for Restarting Secondary Prophylaxis</u>:<br>• Frequent severe recurrences |
| Treatment | <u>Oropharyngeal</u>:<br>• Fluconazole 6–12 mg/kg body weight (maximum 400 mg/dose) by mouth once daily<br>• Clotrimazole troches, 10-mg troche by mouth 4–5 times daily<br>• Nystatin suspension 4–6 mL by mouth 4 times daily, or 1–2, 200,000-unit flavored pastilles by mouth 4–5 times daily<br><br>*Treatment Duration:*<br>• 7 to 14 days<br><br><u>Esophageal Disease</u>:<br>• Fluconazole 6–12 mg/kg body weight by mouth once daily (maximum dose: 600 mg)<br>• Itraconazole oral solution, 2.5 mg/kg body weight/dose by mouth twice daily<br><br>*Treatment Duration:*<br>• Minimum of 3 weeks and for at least 2 weeks following the resolution of symptoms | <u>Oropharyngeal (Fluconazole-Refractory)</u>:<br>• Itraconazole oral solution 2.5 mg/kg body weight/dose by mouth twice daily (maximum 200–400 mg/day)<br><br><u>Esophageal Disease</u>:<br>• Amphotericin B (deoxycholate) 0.3–0.7 g/kg body weight IV once daily<br><br>*Echinocandins*<br>*<u>Anidulafungin</u>:*<br>• *Aged 2–17 Years:* Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV<br>• *Aged ≥18 Years:* 200-mg loading dose, then 100 mg/dose daily IV<br><br>*<u>Caspofungin</u>:*<br>• *Infants Aged <3 Months:* 25 mg/m$^2$ BSA/dose daily IV<br>• *Aged 3 Months–17 Years:* 70 mg/m$^2$/day IV loading dose followed by 50 mg/m$^2$/day IV (maximum 70 mg). Note: Dosing of caspofungin for children should be based on body surface area.<br>• *Aged ≥18 Years:* 70-mg loading dose IV, then 50 mg/dose daily IV | ItrItraconazole oral solution <u>**should not**</u> be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease.<br><br>Central venous catheters should be removed, when feasible, in children with HIV with fungemia.<br><br>In uncomplicated catheter-associated *C. albicans* candidemia, an initial course of amphotericin B followed by fluconazole to complete treatment can be used (use invasive disease dosing).<br><br>Voriconazole has been used to treat esophageal candidiasis in a small number of immunocompromised children without HIV.<br><br><u>Voriconazole Dosing in Pediatric Patients</u>:<br>• Voriconazole 9 mg/kg body weight/dose every 12 hours IV loading for day 1, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours.<br>• Conversion to oral voriconazole should be at 9 mg/kg body weight/dose orally every 12 hours.<br>• Children aged ≥12 years and weighing at least 40 kg can use adult dosing (load voriconazole 6 mg/kg body weight/dose every 12 hours IV on day 1, followed by 4 mg/kg body weight/dose every 12 hours IV. Conversion to oral therapy at 200 mg every 12 hours by mouth). |

**Dosing Recommendations for Prevention and Treatment of Candidiasis** (page 2 of 3)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment, continued | Invasive Disease<br>Critically ill<br>*Echinocandin Recommended*<br>*Anidulafungin:*<br>• *Aged 2–17 Years:* Load with 3 mg/kg body weight/daily dose IV and then maintenance dose at 1.5 mg/kg body weight once daily<br>• *Aged ≥18 Years:* 200-mg loading dose, then 100 mg once daily<br>*Caspofungin:*<br>• *Infants Aged <3 Months:* 25 mg/m² BSA/dose once daily IV<br>• *Aged 3 months*–17 years, 70 mg/m² BSA/day loading dose followed by 50 mg/m² once daily (maximum 70 mg). **Note:** Dosing of caspofungin in children should be based on body surface area.<br>• *Aged ≥18 Years:* 70-mg loading dose, then 50 mg once daily<br>*Micafungin:*<br>• **Note:** In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below). | *Micafungin:*<br>• **Note:** In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below).<br>• *Neonates:* Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations.<br>• *Infants* <15 kg body weight, 5–7 mg/kg body weight/dose daily IV<br>• *Children* ≤40 kg body weight and aged 2–8 years, 3–4 mg/kg body weight/dose daily IV<br>• *Children* ≤40 kg body weight and aged 9–17 years, 2–3 mg/kg body weight/dose daily IV<br>• *Children* >40 kg body weight, 100 mg/dose daily IV<br>*IV Fluconazole:*<br>• *Children:* 6–12 mg/kg body weight/dose daily for infants and children of all ages (maximum dose: 600 mg daily).<br>Invasive Disease:<br>• Fluconazole 12 mg/kg body weight IV once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia)<br>• Lipid formulations of amphotericin B, 5 mg/kg body weight IV once daily<br>• Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily | Anidulafungin in Children Aged 2–17 Years:<br>• Loading dose of 3 mg/kg body weight/once daily followed by 1.5 mg/kg body weight/once daily (100 mg/day maximum).<br>Fluconazole Dosing Considerations:<br>• If a neonate's creatinine level is >1.2 mg/dL for >3 consecutive doses, the dosing interval for fluconazole 12 mg/kg body weight may be prolonged to one dose every 48 hours until the serum creatinine level is <1.2 mg/dL.<br>• *Aged ≥18 Years*: 400 mg/dose once daily (6 mg/kg body weight once daily). |

**Dosing Recommendations for Prevention and Treatment of Candidiasis** (page 3 of 3)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment, continued | • *Neonates:* Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations.<br>• *Infants* <15 kg body weight: 5–7 mg/kg/day<br>• *Children* ≤40 kg body weight and aged 2–8 years: 3–4 mg/kg body weight/dose daily IV<br>• *Children* ≤40 kg body weight and aged 9–17 years: 2–3 mg/kg body weight/dose daily<br>• *Children* >40 kg body weight: 100 mg/dose daily IV<br>*Treatment Duration:*<br>• Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture.<br><u>Not critically ill</u><br>*Fluconazole Recommended:*<br>• 12 mg/kg body weight/dose daily IV (maximum dose: 600 mg) for infants and children of all ages<br>• Avoid fluconazole for *C. krusei* and *C. glabrata*, avoid echinocandin for *C. parapsilosis*.<br>*Treatment Duration:*<br>• Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture. | | |

Key to Abbreviations: BSA = body surface area; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; IV = intravenous; PK = pharmacokinetic

# 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)**.<br>• 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)**.<br>• 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*)**.<br>• For patients with mild disease (e.g., focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate **(BII*)**.<br>• Itraconazole is preferred for treatment of skeletal infections **(AII*)**.<br>• 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)**.<br>• Amphotericin B preparations are not the drugs of choice for treating coccidioidal meningitis; fluconazole is the preferred drug for treating coccidioidal meningitis **(AII*)**.<br>• Lifelong antifungal suppression (secondary prophylaxis) with either fluconazole or itraconazole is recommended for treating HIV-infected children after disseminated, diffuse pulmonary, and/or meningeal coccidioidomycosis **(AII*)**, even if immune reconstitution is achieved with combination antiretroviral therapy (cART). Lifelong secondary prophylaxis should be considered for children with mild disease and CD4 T lymphocyte cell count <250 cells/mm$^3$ or <15%, even if immune reconstitution is achieved with cART **(BIII)**. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***Rating of Evidence:*** *I = One or more randomized trials <u>in children</u>† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies <u>in adults</u> with long-term clinical outcomes with accompanying data <u>in children</u>† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*<br>*† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents* |

## Epidemiology

Coccidioidomycosis is caused by the endemic,[1,2] soil-dwelling dimorphic fungus, *Coccidioides* spp. Two species, *Coccidioides posadasii* and *C. immitis*, have been identified using molecular and biogeographic characteristics. *C. immitis* appears to be confined mainly to California; *C. posadasii* is more widely distributed through the southwestern United States, northern Mexico, and Central and South America. Clinical illnesses caused by each are indistinguishable. Infection usually results from inhalation of spores (arthroconidia) produced by the mycelial form which grows in arid, windy environments with hot summers preceded by rainy seasons.[3,4,5,6] Infection that occurs in non-endemic regions usually results from either re-activation of a previous infection or from acquisition during travel to an endemic region.[7] Contaminated fomites, such as dusty clothing or agricultural products,[8] also have been implicated as infrequent sources of infection.[9]

Most illnesses are primary infections with rates governed by both environmental conditions that are conducive to fungal growth and to activities/conditions that predispose to inhalation of spores. Increased infection rates have been attributed to population shifts to endemic regions, climatic conditions, and better recognition.[10-12] A review of hospitalizations for coccidioidomycosis at children's hospitals from 2002 to 2006 found an increased incidence in 2005 to 2006, especially among patients with comorbid conditions.[13]

Impairment of cellular immunity is a major risk factor for severe primary coccidioidomycosis or relapse of past infection. In HIV-infected adults, both localized pneumonia and disseminated infection usually are observed in individuals with CD4 T lymphocyte (CD4) cell counts <250 cells/mm$^3$.[14,15] The threshold for increased risk in HIV-infected children has not been established; systemic fungal infection has occurred when CD4 counts were ≤100 cells/mm$^3$ and with CD4 percentages <15%, both indicative of severe immunosuppression.[16,17] Although no cases of coccidioidomycosis were reported in HIV-infected children enrolled in the Perinatal AIDS Collaborative Transmission Study, the study sites under-represented geographic regions in which coccidioidomycosis is endemic.[18] Women who acquire coccidioidomycosis late in pregnancy are at risk of dissemination, but infection in their infants is infrequent.[19] Infections in infants usually result from inhalation of spores in the environment. In adults, combination antiretroviral therapy (cART) appears to be responsible for the declining incidence and severity of coccidioidomycosis.[20,21] Data are limited in children.

## Clinical Manifestations

Coccidioidal infection can range from a mild, self-limited, flu-like illness to more severe, focal or disseminated illness, including pneumonia, bone and joint infection and meningitis. Immunocompromised individuals and previously healthy blacks, Hispanics, and Filipinos with coccidioidomycosis are at increased risk of dissemination, as are pregnant women who acquire coccidioidal infection during the second or third trimester[22] or the postpartum period.[23,24] The severity of clinical manifestations in HIV-infected adults varies in direct proportion to the degree of immunocompromise. Diffuse pulmonary infection and extrathoracic dissemination have been associated with decreased CD4 counts, increased HIV RNA levels, and lower likelihood of having received potent antiretroviral therapy (ART).[21] Focal pneumonitis can occur in mild to moderately immunocompromised patients.[15,24] Pleural inflammation may result in effusion, empyema, and/or pneumothorax.[25] If untreated, a coccidioidal antibody-seropositive, HIV-infected individual is at risk of serious disease, with the degree of severity inversely proportional to absolute CD4 counts <250/mm$^3$. Bone and joint involvement is rare in HIV-infected patients.[20,26]

Children with primary pulmonary infection may present with fever, malaise, and chest pain. The presence of cough varies, and hemoptysis is rare. Persistent fever may be a symptom of extrathoracic dissemination. Children with meningitis may present with headaches, altered sensorium, vomiting, and/or focal neurologic deficits.[27-29] Fever is sometimes absent, and meningismus occurs in only 50% of patients. Hydrocephalus complicating basilar inflammation[27,30] occurs in most (83%–100%) children with coccidioidal meningitis.[27,31] Generalized lymphadenopathy, skin nodules, plaques or ulcers,[24,32] peritonitis, and liver abnormalities also may accompany disseminated disease.

## Diagnosis

Because signs and symptoms are non-specific, the diagnosis of coccidioidomycosis should be among those considered in patients who reside in or have visited endemic areas.[25,33] Culture, microscopy, and serology have been the methods used for diagnosis, but newer tests, including coccidioidal galactomannan antigen detection in urine,[1,34] are especially useful for diagnosis in immunocompromised hosts. Polymerase chain reaction (PCR) assays that target specific coccidioidal genes have been developed but are not yet commercially available.[35,36]

In patients with meningitis, cerebrospinal fluid (CSF) shows moderate hypoglycorrhachia, elevated protein concentration, and pleocytosis with a predominance of mononuclear cells. CSF eosinophilia may also be present. The observation of distinctive spherules containing endospores in histopathologic tissue[37] or other clinical specimens is diagnostic. Stains of CSF in patients with meningitis usually are negative. Pyogranulomatous inflammation with endosporulating spherules is seen in affected tissue specimens with haematoxylin and eosin. Spherules can also be observed using Papanicolaou, Gomori methenamine silver nitrate, and periodic acid-Schiff stains. Cytologic stains are less reliable for diagnosing pulmonary coccidioidomycosis, and a negative cytologic stain on a clinical respiratory specimen may not exclude active pulmonary coccidioidomycosis.[26] Potassium hydroxide stains are less sensitive and should not be used.[26]

Growth of *Coccidioides* spp. is supported by many conventional laboratory media used for fungal isolation; growth may occur within 5 days at 30°C to 37°C.[26] Blood cultures are positive in <15% of cases; CSF cultures are positive in <50% of children with meningitis.[24,26,38] Cultures of respiratory specimens are often positive in adults with pulmonary coccidioidomycosis. The laboratory should be alerted to clinical suspicion of coccidioidal infection so that specimens can be handled in secure and contained fashion to minimize hazards to laboratory personnel.

Serologic assays, performed by enzyme-linked immunoassay (EIA), immunodiffusion, or classical tube precipitin or complement fixation methodology that measure coccidioidal Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibody are valuable aids in diagnosis[39] but may be falsely negative in immunocompromised hosts. Presence of IgM-specific coccidioidal antibody suggests active or recent infection although, in instances in which IgG-specific antibody is absent, data are conflicting about potential false positives.[40,41] IgG-specific antibody appears later and persists for 6 to 8 months. A commercial EIA appears more sensitive than the older tube precipitin and complement fixation tests and the immunodiffusion assays, although concern remains about specificity.[42] The EIA, however, is not quantitative.[24] Assays for coccidioidal antibody in serum or body fluids such as CSF provide diagnostic and prognostic information. Cross-reactivity can occur with other endemic mycoses. IgG-specific antibody titers often become undetectable in several months if the infection resolves. The diagnosis of meningitis is established with either a positive CSF culture or detection of IgG-specific antibody in CSF. Serial testing[36] following at least a 2-week interval may be needed to demonstrate this. Antibody titers decline during effective therapy. A *Coccidiodes* EIA has been developed that detects and quantifies coccidioidal galactomannan concentrations in urine samples[34,43,44] and is especially useful in serious infections and/or instances in which antibody is undetectable. Dissociation of immune complexes has increased the sensitivity of detection of coccidioidal antigen in serum.[44] Meningitis has been diagnosed using real-time PCR analysis of CSF.[36]

## Prevention Recommendations

### *Preventing Exposure*

HIV-infected patients who reside in or visit regions in which coccidioidomycosis is endemic cannot completely avoid exposure to *Coccidioides* spp., but risk can be reduced by avoiding activities and/or exposure to sites that may predispose to inhalation of spores. These include disturbing contaminated soil, archaeological excavation, and being outdoors during dust storms. If such activities are unavoidable, use of high-efficiency respiratory filtration devices should be considered.[36]

### *Preventing First Episode of Disease*

No prospective studies have been published that examine the role of prophylaxis to prevent development of active coccidioidomycosis in patients without previous (recognized) episodes of coccidioidomycosis. Although some experts would provide prophylaxis with an azole (fluconazole) to coccidioidal antibody-positive HIV-infected patients living in regions with endemic coccidioidomycosis, others would not.[26] Chemoprophylaxis is used for coccidioidal antibody-positive HIV-infected adults living in endemic areas and with CD4 counts <250 cells/mm$^3$.[45,46] However, given the low incidence of coccidioidomycosis in HIV-infected children, the potential for drug interactions, potential for development of antifungal drug resistance, and the cost, the routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended **(BIII)**.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

In patients with HIV infection, effective cART, if not being administered at the time of diagnosis of coccidioidomycosis, should be started in concert with initiation of antifungal agents. Treatment protocols that are recommended for HIV-infected children are based on experience in nonrandomized, open-label studies in adults. Physicians who infrequently treat children with coccidioidomycosis should consider consulting with experts.

Antifungal therapy had been a recommendation for all HIV-infected adults with clinically active, mild coccidioidomycosis.[47] More recently, treatment protocols appropriate for patients who are HIV-uninfected have been suggested[47] for HIV-infected adults reliably receiving potent ART and who have CD4 counts >250 cells/mm$^3$.[46] That would include patients with mild infections that are not accompanied by signs suggestive of dissemination, diffuse pulmonary infiltrates, or meningitis. In this setting, patients should be closely monitored to ensure compliance with ART, effective HIV suppression, and maintenance of CD4 counts >250 cells/mm$^3$. Management should also include education directed at reducing the probability of re-exposure to coccidioidal spores. In children, absent comparable published experience in this setting, expert consultation should be sought and, if treatment is elected, recommendations should be based upon assurance of continued compliance with ART, confirmation of continued HIV suppression, CD4 counts >250/mm$^3$, education directed at decreasing the likelihood of exposure to coccidioidal spores, and close medical follow up.

For patients with mild, non-meningitic disease (e.g., focal pneumonitis), monotherapy with fluconazole or itraconazole is appropriate given their effectiveness, safety, convenient oral dosing, and pharmacodynamic parameters **(BII*)**. Fluconazole (6–12 mg/kg/day) and itraconazole (5–10 mg/kg/dose twice daily for the first 3 days, followed thereafter by 2–5 mg/kg per dose twice daily) are alternatives to amphotericin B for children who have mild, non-meningitic disease **(BIII)**. In a randomized, double-blind trial in adults, fluconazole and itraconazole were equivalent for treating non-meningeal coccidioidomycosis. Itraconazole (5 mg/kg body weight dose twice daily) appeared to be more effective than fluconazole for treating skeletal infections **(AII*)**.[48]

Severely ill patients with diffuse pneumonia and/or other signs of probable disseminated infection (not involving the CNS) are initially treated with an amphotericin B preparation because these appear to evoke a faster therapeutic response than do the azoles.[49,50] Although there is no evidence that the lipid preparations are more effective than amphotericin B deoxycholate, lipid formulations often are used because they are better tolerated **(AIII)**. The length of amphotericin B therapy is governed by both the severity of initial symptoms and the pace of the clinical improvement. Thereafter, amphotericin B is stopped and treatment with fluconazole or itraconazole begun **(BIII)**. Some experts initiate therapy with both amphotericin B and a triazole, such as fluconazole, in patients with severe disseminated disease and continue the triazole after amphotericin B is stopped **(BIII)**.[26,48] The total duration of therapy should be ≥1 year.[26]

Meningitis is a life-threatening manifestation of coccidioidomycosis and consultation with experts should be considered **(BIII)**. Successful treatment requires an antifungal agent that achieves effective concentrations in CSF. Intravenous amphotericin B achieves poor CSF concentrations and is therefore not recommended for treating coccidioidal meningitis **(AIII)**. The relative safety and comparatively superior ability of fluconazole to penetrate the blood-brain barrier have made it the treatment of choice for coccidioidal meningitis **(AII*)**. An effective dose of fluconazole in adults is 400 mg/day, but some experts begin therapy with 800 to 1000 mg/day.[47] Children usually receive 12 mg/kg/dose once daily (800 mg/day maximum) **(AII*)**.[51,52] The 12 mg/kg dosage may be required to attain serum concentrations equivalent to those in adults receiving 400 mg/day.[53] Some experts would begin at a dose of 15 to 23 mg/kg/day.[24] Successful therapy with posaconazole[54] and voriconazole has been described in adults but there is no published experience in children.[55] Some experts use amphotericin B administered intrathecally[50,56] in addition to an azole. Intrathecal amphotericin administration adds additional toxicity and is not used as part of initial therapy **(CIII)**. Despite the benefits afforded by the azoles for treating meningitis, a retrospective analysis of outcomes in adults treated for coccidioidal meningitis in the pre-azole (earlier than 1980) compared with outcomes in the azole era found that a similar percentage developed serious complications, including stroke and hydrocephalus; risk factors for acquiring coccidioidal meningitis in the azole era included immunocompromised state, with one-third of patients in this group having HIV/AIDS.[28]

## *Monitoring and Adverse Events (Including IRIS)*

In addition to monitoring patients for clinical improvement, some experts[26] have recommended monitoring coccidioidal IgG antibody titers to assess response to therapy. Titers should be obtained every 12 weeks **(AIII)**. If therapy is succeeding, titers should decrease progressively; a rise in titers suggests recurrence of clinical disease. However, if serologic tests initially were negative, titers during effective therapy may increase briefly and then decrease.[26] This lag in response during the first 2 months of therapy should not necessarily be construed as treatment failure.

Adverse effects of amphotericin B are primarily those associated with nephrotoxicity. Infusion-related fevers, chills, nausea, and vomiting also can occur, although they are less frequent in children than in adults. Lipid formulations of amphotericin B have lower rates of nephrotoxicity. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur (see discussion on monitoring and adverse events in *Candida* infection). Intrathecal injection of amphotericin B may result in arachnoiditis.[57,58]

Triazoles can interact with other drugs metabolized by CYP450-dependent hepatic enzymes,[59,60] and the potential for drug interactions should be assessed before initiation of therapy **(AIII)**. Use of fluconazole or itraconazole appears to be safe in combination with ART. Voriconazole should be avoided in patients receiving protease inhibitors **(BIII)**[61] or non-nucleoside reverse transcriptase inhibitors.[15] The most frequent adverse effects of fluconazole are nausea and vomiting. Skin rash and pruritus may be observed, and cases of Stevens-Johnson syndrome have been reported. Asymptomatic increases in transaminases occur in 1% to 13% of patients receiving azole drugs. In HIV-infected patients, fluconazole at high doses can cause adrenal insufficiency.[62]

Because absorption of itraconazole varies from patient to patient, serum concentrations should be measured to ensure effective, non-toxic levels of drug, monitor changes in dosage, and assess compliance **(BIII)**.

Coccidioidomycosis-associated immune reconstitution inflammatory syndrome following the initiation of ART has not been reported in children and is rarely reported in adults.[63]

## *Managing Treatment Failure*

The treatment of coccidioidomycosis unresponsive to standard therapy has been reviewed; the majority of experience has been in adults.[55] Posaconazole was effective in 6 adults with disease refractory to treatment with other azoles and to amphotericin B[64] and has been used successfully in 73% of 15 adults whose infections were refractory to previous therapy.[65] Posaconazole has also been effective for chronic refractory meningitis unresponsive to fluconazole.[54] Voriconazole was effective in treating coccidioidal meningitis and non-meningeal disseminated disease in adults who did not respond to fluconazole or were intolerant of amphotericin B.[66,67,68] Monotherapy with caspofungin successfully treated disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and other adults in whom conventional therapy failed.[69,70] Others have used caspofungin in combination with fluconazole.[71]

Adjunctive interferon-gamma (IFN-γ)[72] was successfully used in a critically ill adult with respiratory failure who did not respond to amphotericin B preparations and fluconazole.[73] However, no controlled clinical studies or data exist for children; thus, adjunctive IFN-γ is not recommended for use in HIV-infected children **(BIII)**.

In instances in which patients with coccidioidal meningitis fail to respond to treatment with azoles, both systemic amphotericin B and direct instillation of amphotericin B into the intrathecal, ventricular, or intracisternal spaces, with or without concomitant azole treatment, have been used successfully. These regimens are recommended in such instances **(AIII)**.[48,52] The basilar inflammation that characteristically accompanies coccidioidal meningitis often results in obstructive hydrocephalus requiring placement of a CSF shunt. Thus, development of hydrocephalus in coccidioidal meningitis does not necessarily indicate treatment failure. Response rates with the azoles can be excellent, but cures are infrequent. Relapse after cessation of therapy is common, occurring in as many as 80% of patients.[74] Thus, indefinite continuation of fluconazole therapy is recommended for patients who have coccidioidal meningitis **(AII*)**.

### *Preventing Recurrence*

Lifelong suppression (secondary prophylaxis) is recommended for patients following successful treatment of meningitis. Relapse after successful treatment of disseminated coccidioidomycosis can occur and lifelong antifungal suppression with either fluconazole or itraconazole should be used **(AII*)**. Secondary prophylaxis should be considered for children with mild disease and ongoing CD4 counts <250 cells/mm$^3$ or CD4 percentages <15% **(BIII)**.[26,47,49,75,76]

### *Discontinuing Secondary Prophylaxis*

In disseminated infection, continued suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is recommended after completion of initial therapy. Patients with diffuse pulmonary disease, disseminated disease, or meningeal infection should remain on lifelong prophylaxis—even if immune reconstitution is achieved with ART[26]—because of high risk of relapse **(AII*)**. In HIV-infected adults with focal coccidioidal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 counts >250 cells/mm$^3$ on ART, some experts would discontinue secondary prophylaxis after 12 months of antifungal therapy with careful monitoring for recurrence with chest radiographs and coccidioidal serology. However, only a small number of patients have been evaluated, and the safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children has not been studied. Therefore, in HIV-infected children, once secondary prophylaxis is initiated for an acute episode of milder, non-meningeal coccidioidomycosis, lifelong suppressive therapy should be considered, regardless of ART and immune reconstitution **(BIII)**.

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## Dosing Recommendations for Prevention and Treatment of Coccidioidomycosis

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis** | N/A | N/A | Primary prophylaxis not routinely indicated in children. |
| **Secondary Prophylaxis** | Fluconazole 6 mg/kg body weight (maximum 400 mg) by mouth once daily | Itraconazole 2–5 mg/kg body weight (maximum 200 mg) by mouth per dose twice daily | Lifelong secondary prophylaxis with fluconazole for patients with meningitis or disseminated disease in the immunocompromised patient is recommended. Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm$^3$ or CD4 percentage <15%. |
| **Treatment** | Severe Illness with Respiratory Compromise due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease:<br>• Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily, until clinical improvement.<br>• A lipid amphotericin B preparation can be substituted at a dose of 5 mg/kg body weight IV once daily (dosage of the lipid preparation can be increased to as much as 10 mg/kg body weight IV once daily for life-threatening infection).<br>• After the patient is stabilized, therapy with an azole (fluconazole or itraconazole) can be substituted and continued to complete a 1-year course of antifungal therapy.<br><br>Meningeal Infection:<br>• Fluconazole 12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily followed by secondary lifelong prophylaxis.<br><br>Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia):<br>• Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily. | Severe Illness with Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease (If Unable to Use Amphotericin):<br>• Fluconazole 12mg/kg body weight (maximum 800 mg) per dose IV or by mouth once daily<br>• Treatment is continued for total of 1 year, followed by secondary prophylaxis.<br><br>Meningeal Infection (Unresponsive to Fluconazole):<br>• IV amphotericin B plus intrathecal amphotericin B followed by secondary prophylaxis. **Note:** Expert consultation recommended.<br><br>Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia):<br>• Itraconazole 2–5 mg/kg body weight per dose (maximum dose 200 mg) per dose IV or by mouth 3 times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) by mouth per dose twice daily thereafter.<br>• Duration of treatment determined by rate of clinical response. | Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful.<br><br>Itraconazole is the preferred azole for treatment of bone infections.<br><br>Some experts initiate an azole during amphotericin B therapy; others defer initiation of the azole until after amphotericin B is stopped.<br><br>For treatment failure, can consider voriconazole, caspofungin, or posaconazole (or combinations). However, experience is limited and definitive pediatric dosages have not been determined.<br><br>Options should be discussed with an expert in the treatment of coccidioidomycosis.<br><br>Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease and is continued lifelong for meningeal disease.<br><br>Therapy with amphotericin results In a more rapid clinical response in severe, non-meningeal disease. |

**Key to Abbreviations:** CD4 = CD4 T lymphocyte; IV = intravenous

# 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/mm$^3$ 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/mm$^3$ **(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-naive 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)**.

***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*

Given the low incidence of cryptococcosis in HIV-infected children, even during the era before combination antiretroviral therapy (cART), management of this disease in this age group has not been prospectively studied. Treatment recommendations largely reflect information extrapolated from many well-designed studies involving HIV-infected adults with cryptococcal meningitis.[1]

## Epidemiology

Most cases of cryptococcosis in HIV-infected patients are caused by *Cryptococcus neoformans*; *Cryptococcus gattii* (formerly *Cryptococcus neoformans variety gattii*) infection occurs primarily in tropical and subtropical areas. Cryptococcal infections occur much less frequently in HIV-infected children than in adults.[2-5] During the pre-cART era, most cases of cryptococcosis in HIV-infected children (overall incidence, 1%) occurred in those aged 6 through 12 years and in those with CD4 T lymphocyte (CD4) cell counts indicating severe immunosuppression.[4] Access to cART has further decreased the overall incidence of cryptococcal infection[6,7] in HIV-infected children. Data from Pediatric AIDS Clinical Trials Group studies before and after the advent of cART indicate that the rate of invasive fungal infection, including cryptococcosis, has remained <0.1 per 100 child-years.[8,9]

## Clinical Manifestations

Cryptococcosis often presents with subtle and non-specific findings, such as fever and headache. Early diagnosis requires consideration of this infection in symptomatic patients whose CD4 counts indicate severe immunosuppression. In both HIV-infected adults and children, meningoencephalitis is the most common initial manifestation of cryptococcosis. The disease typically evolves over days to weeks with fever and headache. Less frequent findings include nuchal rigidity, photophobia, and focal neurologic signs, as were seen among 30 HIV-infected children with cryptococcosis reported from the United States.[4] In contrast to this indolent presentation, children in Zimbabwe presented with an acute form of neurologic cryptococcosis (69% with nuchal rigidity, 38% with seizure activity, and 23% with focal neurologic signs).[10] *C. gattii* infections occur mostly in people who are not HIV-infected (or do not have other immunocompromsing conditions), and neurologic disease due to *C. gattii* in such apparently normal hosts responds more slowly to treatment and results in high risk of neurologic complications.[11] *C. gattii* infections in HIV-infected patients, however, are uncommon and are similar in presentation to *C. neoformans* infections in HIV-infected hosts.[12]

Disseminated cryptococcosis can be associated with cutaneous lesions, including small, translucent, umbilicated papules (indistinguishable from molluscum contagiosum), nodules, ulcers, and infiltrated plaques resembling cellulitis. Pulmonary cryptococcosis without dissemination is unusual in children. Presenting findings include unexplained recurrent fever, cough with scant sputum, intrathoracic lymphadenopathy, and focal or diffuse pulmonary infiltrates. The infection also can be asymptomatic, with pulmonary nodules revealed on routine chest radiograph.[3]

## Diagnosis

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

A lumbar puncture should be done in any patient with suspected cryptococcal meningitis. CSF cell count, glucose, and protein can be virtually normal with central nervous system (CNS) cryptococcosis, but the opening pressure usually is elevated. Microscopic examination of CSF on India ink-stained wet mounts can be performed to diagnose suspected CNS disease but is largely replaced with the use of the cryptococcal antigen test. In more than 90% of patients with cryptococcal meningitis, cryptococcal antigen can be detected in CSF or serum by latex agglutination test (available from several manufacturers).

Fungal cultures from CSF, sputum, and blood can identify the organism. In some cases (meaning refractory or relapsed disease), susceptibility testing of the *C. neoformans* isolate can be beneficial. Overall, *in vitro* resistance to antifungal agents remains uncommon.[13]

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

## Prevention Recommendations

### *Preventing Exposure*

No strategies have been proven to prevent exposure. *C. neoformans* infection is believed to be acquired through inhalation of aerosolized particles from the environment. Serologic studies of immunocompetent children in an urban setting indicate that most children have been infected by *C. neoformans* by the third year of life.[14]

## *Preventing the First Episode of Disease*

Because the incidence of cryptococcal disease is so low in HIV-infected children,[2-4,15] routine testing of asymptomatic children for serum cryptococcal antigen is not recommended **(CIII)**.

A review of randomized controlled trials using antifungal interventions for the primary prevention of cryptococcal diseases indicates that fluconazole and itraconazole can reduce cryptococcal disease in adults who have advanced HIV disease and severe immunosuppression (CD4 count <50 cells/mm$^3$).[16] However, neither of these interventions clearly affected mortality.

In addition, routine use of antifungal medications is not recommended for primary prophylaxis of cryptococcal infections in children because of the low incidence of cryptococcosis in HIV-infected children, lack of survival benefits in primary prevention studies of adults,[16] possibility of drug interaction, potential resistance to antifungal drugs, and cost **(BIII)**. Early diagnosis of HIV infection and treatment with cART (following current HIV treatment guidelines) to prevent or reverse immune suppression should further reduce risk of cryptococcal disease in HIV-infected children.

## *Discontinuing Primary Prophylaxis*

Not applicable.

# Treatment Recommendations

## *Treating Disease*

**Note:** These recommendations are largely based on high-quality evidence from studies in adults.

### CNS Disease

The most common and well-studied presentation of cryptococcal infection in HIV-infected patients is CNS disease. In light of studies in adults,[17-19] 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 children **(AI*)**. Amphotericin B lipid complex is an alternative to amphotericin B deoxycholate **(BII*)**.[20] CSF was sterilized significantly more rapidly in adults with CNS cryptococcal disease who received initial therapy with amphotericin B deoxycholate (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) than in those who received amphotericin B deoxycholate alone, amphotericin B deoxycholate plus fluconazole, or triple-antifungal therapy.[21,22] In one study of adults, liposomal amphotericin B (AmBisome®) dosed at 4 mg/kg/day resulted in significantly earlier CSF culture conversion than did amphotericin B deoxycholate at 0.7 mg/kg/day.[23] However, a randomized, double-blind clinical trial before the routine availability of cART that compared amphotericin B (0.7 mg/kg/day), liposomal amphotericin B (3 mg/kg/day), and liposomal amphotericin B (6 mg/kg/day) showed no difference in efficacy among the three arms, but significantly fewer adverse events with liposomal amphotericin B (3 mg/kg body weight/day).[24] Cost considerations aside (liposomal amphotericin is significantly more expensive than amphotericin B deoxycholate), based on the reported experience in adults, liposomal amphotericin B would be preferable to amphotericin B deoxycholate in patients with cryptococcal meningitis who have or are at risk of renal failure **(AI*)**. Amphotericin B lipid complex is another option **(BII*)**.[20] Monitoring for and managing increased intracranial pressure (ICP) is crucial to optimal management of CNS cryptococcosis (see below).

In patients who cannot tolerate flucytosine (or if flucytosine is not available), amphotericin B deoxycholate (or its liposomal preparation) with or without fluconazole can be used for initial therapy **(BI*)**. In a randomized Phase II trial in HIV-infected adolescents and adults, amphotericin B deoxycholate plus high-dose fluconazole (800 mg daily) was found to be well tolerated and with a trend toward better outcome at days 42 and 70, compared with amphotericin B deoxycholate alone.[25] Studies are needed to further validate the use of this combination. In another study 80 HIV-seropositive, antiretroviral (ARV)-naive adults presenting with cryptococcal meningitis were randomized to 4 treatment arms of 2-week duration: group 1, amphotericin B (0.7–1 mg/kg) and flucytosine (25 mg/kg 4 times daily); group 2, amphotericin B (0.7–1 mg/kg) and fluconazole (800 mg daily); group 3, amphotericin B (0.7–1 mg/kg) and fluconazole (600 mg twice daily); and group 4, amphotericin B (0.7–1 mg/kg) and voriconazole (300 mg twice daily). The primary end point was the rate of clearance of infection from CSF or early fungicidal activity, as determined by results of serial, quantitative CSF cryptococcal cultures. There were no statistically significant differences in the rate of clearance of cryptococcal colony-forming units (CFU) in CSF samples among the 4 treatment groups.[26] Fluconazole plus flucytosine is superior to fluconazole alone[27,28] and provides an alternative to amphotericin B deoxycholate for acute therapy of invasive disease **(BII*)** that should be used only if amphotericin B-based therapy is not tolerated. Although fluconazole monotherapy was an effective alternative to amphotericin B in adults with AIDS-associated cryptococcal meningitis,[29] concerns in this study about differences in early death, delayed CSF sterilization, and drug resistance[30,31] make fluconazole monotherapy less favorable for initial therapy of CNS disease. Because of rapidly developing resistance, flucytosine alone should never be used to treat cryptococcosis. Echinocandins are not active against cryptococcal infections and should not be used **(AIII)**.

After a minimum of 2 weeks of induction therapy with evidence of clinical improvement and a negative CSF culture after repeat lumbar puncture, amphotericin B deoxycholate (or its liposomal preparation) and flucytosine can be discontinued and consolidation therapy for a minimum of 8 weeks initiated with fluconazole **(AI*)**.[32] Itraconazole is a less preferable alternative to fluconazole for the consolidation phase of CNS therapy **(BI*)**. Fluconazole is preferred because studies comparing the two agents demonstrate higher rates of CSF sterilization during consolidation therapy[18] and less frequent relapse[32] during maintenance therapy in fluconazole recipients. After completion of consolidation therapy, secondary prophylaxis (maintenance therapy or suppressive therapy) should be initiated (see below).

### Pulmonary and Extra Pulmonary Cryptococcosis (CNS Disease Ruled Out)

No controlled clinical studies describe the outcome of non-CNS cryptococcosis in HIV-infected patients. CNS disease should be ruled out in all patients, after which the choice of antifungal medication and length of initial therapy can be decided in light of the clinical severity of illness. Patients with severe pulmonary disease or disseminated cryptococcosis should be treated with a form of amphotericin B with or without the addition of flucytosine, as for CNS disease **(AIII)**. Usually combination therapy should be provided until symptoms resolve. Those with mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy **(AIII)**. Regardless of the antifungal agent selected for initial therapy, secondary prophylaxis with fluconazole or itraconazole should be provided as for CNS disease **(AIII)** (see notes below on secondary prophylaxis).

## *Monitoring and Adverse Events (Including IRIS)*

### Monitoring for Raised Intracranial Pressure

At the time of diagnosis and on subsequent lumbar punctures, all patients with cryptococcal meningitis should have their lumbar opening pressure measured. Studies in adults clearly show the role of increased ICP in deaths associated with CNS cryptococcosis.[18,33] Patients with severe headache, confusion, blurred vision, papilledema, or other neurologic signs or symptoms of increased ICP should be managed using measures to decrease ICP. One approach recommended for adults is to measure pressure continually or repeatedly during the lumbar puncture procedure and to remove CSF until the pressure is approximately half the opening pressure but still no lower than normal.[34] This may be repeated as often as every day until symptoms and signs consistently improve. Similar data describing experience with therapeutic lumbar punctures in children with cryptococcal meningitis are not available. Not specific to cryptococcal meningitis, a cutoff opening pressure of 28 cm of water has been proposed in children, above which the pressure should be considered elevated.[35] CSF shunting through a lumbar drain or ventriculostomy can be considered for patients who continue to have symptomatic increased ICP despite multiple lumbar taps **(BIII)**. Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis and most experts would not recommend their use in children **(CIII)**. Acetazolamide is hazardous as therapy for increased ICP management in adults without signs of immune reconstitution inflammatory syndrome (IRIS) and has not been evaluated in children with cryptococcal meningitis; acetazolamide is **not** recommended for adults and most experts would similarly not use it in children **(BIII)**.

### Monitoring Treatment Response

In addition to monitoring clinical response, mycological response in patients with CNS cryptococcosis typically is assessed by a repeat lumbar puncture and CSF examination at 2 weeks of treatment, with continuation of induction therapy until CSF culture is negative.

Monitoring serial serum cryptococcal antigen titers is not useful for following treatment efficacy because changes in serum cryptococcal antigen titers do not correlate well with outcome during treatment for acute meningitis or during suppressive therapy.[36,37] Serial measurement of CSF cryptococcal antigen is more useful; in one study, an unchanged or increased titer of antigen in CSF correlated with clinical and microbiologic treatment failure, and a rise in CSF antigen titer during suppressive therapy was associated with relapse of cryptococcal meningitis.[36] However, monitoring of CSF cryptococcal antigen levels requires repeated lumbar punctures and is not routinely recommended for monitoring response.

### Monitoring for Adverse Events

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

Flucytosine has the potential for marked toxicity, especially affecting the bone marrow (meaning anemia, leukopenia, and thrombocytopenia), liver, gastrointestinal (GI) tract, kidney, and skin. In patients receiving flucytosine, flucytosine blood levels should be monitored to prevent bone marrow suppression and GI toxicity; after 3–5 days of therapy, the target 2-hour post-dose serum level of flucytosine is 40–60 µg/mL. Flucytosine should be avoided in children with severe renal impairment.

Fluconazole and the other azoles have relatively low rates of toxicity, but their potential drug interactions can limit their use. Because of their ability to inhibit the CYP450-dependent hepatic enzymes, the potential for drug interactions, particularly with ARV drugs, should be carefully evaluated before initiation of therapy. Liver function tests should be monitored during treatment.

### Immune Reconstitution Inflammatory Response Syndrome (IRIS)

While cases of IRIS in HIV-infected children have been described,[38] most of the available information comes from adult literature.

IRIS related to cryptococcosis can present within weeks (such as meningitis) or months (such as lymphadenitis) after start of cART. Symptoms of meningitis are similar to those described for meningitis presenting as the initial manifestation of cryptococcosis. In one study, about 30% of all HIV-infected adults hospitalized for infection with *C. neoformans* who received cART were re-admitted with symptoms attributed to an inflammatory response.[39] Of the 18 patients with *C. neoformans*-related IRIS in the cited study, 17 had culture-negative meningitis, and most cases occurred during the first 30 days after initiation of cART. The most common presentation of late cryptococcal IRIS is lymphadenitis, particularly mediastinal lymphadenitis.[40,41]

IRIS is a clinical diagnosis. While there are no specific laboratory tests to diagnose IRIS, presence of negative cultures in a patient with clinical signs suggestive of tissue inflammation in the face of rapidly improving cellular immunity would be suggestive of IRIS over treatment failure. The optimal management of cryptococcal IRIS has not been defined. Antifungal therapy should be initiated in patients not already receiving it, raised intracranial pressure managed if present and antiretroviral therapy (ART) should be continued. Although many cases resolve spontaneously, some experts also have used anti-inflammatory therapy (e.g., short-course corticosteroids) in patients with severely symptomatic IRIS **(CIII)**.[40,42]

Adult HIV-infected treatment-naive patients with cryptococcal meningitis who go on to develop IRIS after starting cART are more likely to have higher HIV RNA levels at baseline[43] and exhibit less initial CSF inflammation at the time of cryptococcal meningitis diagnosis, compared with those who do not develop IRIS.[44] In patients with advanced immunosuppression and non-tuberculous opportunistic infections (OIs), the presence of a fungal infection, lower CD4 counts and higher HIV RNA levels at baseline, and higher CD4 counts and lower HIV RNA levels on treatment were found associated with IRIS.[43] For patients not on cART at the time of diagnosis of cryptococcal meningitis, the timing of cART in relation to antifungal treatment remains controversial. One randomized trial of adult HIV-infected patients with OIs (excluding tuberculosis) primarily from the United States that included 35 patients with cryptococcal meningitis suggested that early cART treatment (within the first 14 days of diagnosis) was safe and resulted in less AIDS progression/death compared to deferred cART.[45] However a randomized clinical trial in Zimbabwe was reported to show higher mortality in patients receiving cART starting within 72 hours of diagnosis compared to those waiting at least 10 weeks to initiate ART.[46] Patients in this study were treated with high dose fluconazole. Differences in management of cryptococcal meningitis, raised ICP, and cART treatment options may account for some of the differences between these two studies. In ARV-naive patients newly diagnosed with cryptococcal meningitis or disseminated disease, delay in potent ART may be prudent until the end of the first 2 weeks of induction therapy **(CIII)**; further delays in initiating cART, especially in resource-poor settings, should be individualized.

## *Managing Treatment Failure*

Treatment failure is defined as worsening or lack of improvement in signs and symptoms after 2 weeks of appropriate therapy, including management of ICP; or relapse after an initial clinical response. Differentiating IRIS from treatment failure is important because treatment approaches and outcomes differ; persistent positive cultures indicate treatment failure. Optimal management of patients with treatment failure is unknown. If cultures remain positive, evaluation of antifungal susceptibilities can be considered, although *C. neoformans* resistance to fluconazole is rare in the United States. Patients in whom initial azole-based therapy fails should be switched to amphotericin B-based therapy,[30] ideally in combination with flucytosine; the possibility of drug interactions resulting in sub-therapeutic azole levels (meaning concurrent rifampin use or other drugs metabolized by the liver) should be explored.[30] Use of liposomal amphotericin B should be considered, because one study suggests improved efficacy in CSF sterilization with liposomal preparations than with standard amphotericin B.[23] Some data from HIV-infected adults indicate higher dosages (meaning 400–800 mg/day) of fluconazole in combination with flucytosine also can be considered for salvage therapy.[19,47] Clinical experience with new antifungal agents in managing cryptococcosis is limited. A few patients with cryptococcal infections refractory or intolerant to standard antifungal therapy have been treated with posaconazole or voriconazole with variable success.[48,49]

## *Preventing Recurrence (Secondary Prophylaxis)*

Patients who have completed initial therapy for cryptococcosis should receive secondary prophylaxis (maintenance therapy or suppressive therapy) **(AI*)**. Fluconazole **(AI*)** is superior and preferable to itraconazole **(BI*)** for preventing relapse of cryptococcal disease.[32,50,51]

## *Discontinuing Secondary Prophylaxis (Maintenance or Suppressive Therapy)*

Until recently, lifelong secondary prophylaxis typically was recommended. The safety of discontinuing secondary prophylaxis for cryptococcosis after immune reconstitution with cART has not been studied in children, and decisions in that regard should be made on a case-by-case basis. Adults who have successfully completed a course of initial therapy (including ≥12 months of secondary prophylaxis), remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained (≥6 months) increase in their CD4 counts to ≥100 cells/mm$^3$ with an undetectable viral load on ART for >3 months after cART are at apparent low risk of recurrence of cryptococcosis.[52-54] In light of these observations and inference from data regarding discontinuing secondary prophylaxis for other OIs in adults with advanced HIV infection, discontinuing secondary prophylaxis for cryptococcosis (after receiving secondary prophylaxis for at least 1 year) can be considered for asymptomatic children aged ≥6 years, with increase in their CD4 counts to ≥100 cells/mm$^3$ and an undetectable viral load on cART for ≥3 months **(CIII)**. Secondary prophylaxis should be re-initiated if the CD4 count decreases to <100 cells/mm$^3$ **(AIII)**. Most experts would not discontinue secondary prophylaxis for patients younger than age 6 years **(CIII)**.

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### Dosing Recommendations for Prevention and Treatment of Cryptococcosis (page 1 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis** | Not recommended | Not recommended | N/A |
| **Secondary Prophylaxis**[a] | Fluconazole 6 mg/kg body weight (maximum 200 mg) by mouth once daily | Itraconazole oral solution 5 mg/kg body weight (maximum 200 mg) by mouth once daily | Secondary Prophylaxis Indicated:<br>• Documented disease<br>Criteria For Discontinuing Secondary Prophylaxis<br>*If **All** of the Following Criteria are Fulfilled:*<br>• Age ≥6 years<br>• Asymptomatic on ≥12 months of secondary prophylaxis<br>• CD4 count ≥100 cells/mm$^3$ with undetectable HIV viral load on cART for >3 months<br>Criteria for Restarting Secondary Prophylaxis:<br>• CD4 count <100/mm$^3$ |
| **Treatment** | CNS Disease<br>*Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy):*<br>• Amphotericin B deoxycholate 1.0 mg/kg body weight (or liposomal amphotericin B 6 mg/kg body weight) IV once daily **PLUS** flucytosine 25 mg/kg body weight per dose by mouth given 4 times daily | CNS Disease<br>*Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)*<br>*If Flucytosine Not Tolerated or Unavailable:*<br>• **A.** Liposomal amphotericin B, 6 mg/kg body weight IV once daily, **or** Amphotericin B Lipid Complex, 5 mg/kg body weight IV once daily, **or** Amphotericin B deoxycholate, 1.0–1.5 mg/kg body weight IV once daily **alone or B. in combination** with high-dose fluconazole (12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight [max 800 mg] IV). **Note:** Data-driven pediatric dosing guidelines are unavailable for fluconazole with use of such combination therapy. | In patients with meningitis, CSF culture should be negative prior to initiating consolidation therapy.<br>Overall, *in vitro* resistance to antifungal agents used to treat cryptococcosis remains uncommon. Newer azoles (voriconazole, posaconazole, ravuconazole) are all very active *in vitro* against *C. neoformans*, but published clinical experience on their use for cryptococcosis is limited. |

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Treatment,** continued | *Consolidation Therapy (Followed by Secondary Prophylaxis):*<br>• Fluconazole 12 mg/kg body weight on day 1, then 10–12 mg/kg body weight (max 800 mg) once daily IV or by mouth for a minimum of 8 weeks | *If Amphotericin B-Based Therapy Not Tolerated:*<br>• Fluconazole, 12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily **PLUS** flucytosine, 25 mg/kg body weight per dose by mouth given 4 times daily<br>*Consolidation Therapy (followed by secondary prophylaxis):*<br>• Itraconazole 5–10 mg/kg body weight by mouth given once daily, or 2.5–5 mg/kg body weight given twice daily (maximum 200 mg/dose) for a minimum of 8 weeks. A loading dose (2.5–5 mg/kg body weight per dose 3 times daily) is given for the first 3 days (maximum 200 mg/dose; 600 mg/day). See comment on itraconazole under Other Options/Issues. | Liposomal amphotericin and amphotericin B lipid complex are especially useful for children with renal insufficiency or infusion-related toxicity to amphotericin B deoxycholate.<br>Liposomal amphotericin and amphotericin B lipid complex are **significantly more expensive than amphotericin B deoxycholate**.<br>Liquid preparation of itraconazole (if tolerated) is preferable to tablet formulation because of better bioavailability, but it is more expensive. Bioavailability of the solution is better than the capsule, but there were no upfront differences in dosing range based on preparation used. Ultimate dosing adjustments should be guided by itraconazole levels. |
| | Localized Disease, Including Isolated Pulmonary Disease (CNS Not Involved)[b]:<br>• Fluconazole 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily<br>Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[b]:<br>• Amphotericin B 0.7–1.0 mg/kg body weight, or<br>• Liposomal amphotericin, 3–5 mg/kg body weight, or<br>• Amphotericin B lipid complex 5 mg/kg body weight IV once daily (± flucytosine) | Localized Disease Including Isolated Pulmonary Disease (CNS Not Involved)[b]:<br>• Amphotericin B, 0.7–1.0 mg/kg body weight, or<br>• Amphotericin liposomal 3–5 mg/kg body weight, or<br>• Amphotericin lipid complex, 5 mg/kg body weight IV once daily<br>Disseminated disease (CNS not involved) or severe, pulmonary disease[b]:<br>• Fluconazole, 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily | Serum itraconazole concentrations should be monitored to optimize drug dosing.<br>Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake, or impair its renal excretion, or both.<br>Flucytosine dose should be adjusted to keep 2-hour post-dose drug levels at 40–60 µg/mL<br>Oral acetazolamide **should not** be used for reduction of ICP in cryptococcal meningitis.<br>Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis.<br>Secondary prophylaxis is recommended following completion of initial therapy (induction plus consolidation)—drugs and dosing listed above. |

[a] Secondary prophylaxis is also referred to as maintenance therapy or suppressive therapy.

[b] Duration of therapy for non-CNS disease depends on site and severity of infection and clinical response

**Key to Acronyms:** cART = combination antiretroviral therapy; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous

# Cryptosporidiosis (Last updated August 29, 2019; last reviewed August 29, 2019)

| Panel's Recommendations |
|---|
| I. **In children with HIV infection, what are the best interventions (compared with no intervention) to prevent episodes of cryptosporidiosis?** |
| • Cryptosporidiosis can be prevented by practicing good hygiene (e.g., frequent handwashing), avoiding drinking water that might be contaminated, avoiding high-risk swimming exposures (e.g., drinking swimming water, especially in pools and water playgrounds frequented by very young children), and not eating food that might be contaminated (**expert opinion**). |
| • Children with HIV infection should avoid contact with pre-weaned bovine calves, lambs, goat kids, ill animals, young dogs and cats, stray animals, and animal or human feces or any feces-contaminated surfaces (**expert opinion**). |
| • In children with HIV infection, combination antiretroviral therapy (ART) to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric cryptosporidiosis (**strong**, **low**). |
| II. **In children with HIV infection, what are the best interventions (compared with no intervention) to treat cryptosporidiosis?** |
| • Effective ART is the primary initial treatment for cryptosporidiosis in children (**strong**, **moderate**). |
| • Nitazoxanide, in addition to ART, can be considered to treat cryptosporidiosis in children with HIV infection (**strong**, **moderate**). |
| • Dehydration and electrolyte abnormalities should be corrected, and nutritional support should be provided as appropriate (**expert opinion**). |
| Rating System<br>*Strength of Recommendation:* Strong; Weak<br>*Quality of Evidence:* High; Moderate; Low; or Very Low |

## Epidemiology

*Cryptosporidium* spp. are protozoan parasites that primarily cause enteric illness (i.e., diarrhea) in humans and animals. *Cryptosporidium* spp. are distributed worldwide, and some species lack strict host specificity. The two species that infect humans most frequently are *Cryptosporidium hominis* and *Cryptosporidium parvum*. In addition, infections caused by *Cryptosporidium meleagridis*, *Cryptosporidium felis*, and *Cryptosporidium canis* have been reported in people with HIV infection. Among adults with HIV infection, risk of morbidity associated with *Cryptosporidium* infection is greatest in those with advanced immunosuppression, typically CD4 T lymphocyte (CD4) cell counts <100/mm$^3$.[1-3] *Cryptosporidium* primarily infects the distal small intestine and colon, but in immunocompromised hosts, extraintestinal involvement has been documented.

Infection occurs after ingestion of infectious oocysts that were excreted in the feces of infected animals and humans. The parasite is highly infectious, with an $ID_{50}$ (median dose that will infect 50% of those exposed to the parasite) ranging from 9 to 1,042 oocysts for *C. parvum*,[4] and 10 to 83 oocysts for *C. hominis*.[5] Infection occurs when the ingested oocysts release sporozoites, which attach to and invade the intestinal epithelial cells. The parasite preferentially infects the ileum and colon.

Contact with infected persons (particularly children in diapers or in child care settings) or infected animals (particularly pre-weaned calves) is an important cryptosporidiosis risk factor.[6-11] *Cryptosporidium* oocysts can contaminate recreational water sources (such as swimming pools, water parks, and lakes) and drinking water supplies and cause infection when contaminated water is ingested. Oocysts are environmentally hardy and extremely chlorine tolerant. They can persist for days in swimming pools despite standard chlorination, and typical pool filtration systems do not efficiently remove oocysts. Multi-step treatment processes can be used to remove (i.e., flocculation and filtration) and inactivate (e.g., ultraviolet treatment) oocysts to protect public drinking water supplies and recreational water. Foodborne transmission, particularly involving unpasteurized apple cider, raw milk, and ill food handlers, has been documented. International travelers who drink the water in countries with less stringent drinking water treatment standards than the United States may might be at risk for *Cryptosporidium* infection.

In a serosurvey of multiple U.S. cities, 21.3% of children aged <10 years and 21.5% of those aged 11 to 20 years had detectable response to *Cryptosporidium* antigen.[12] Among immunocompetent pediatric patients with diarrhea in Oklahoma, 38% of those aged 5 to 13 years and 58% of those aged 14 to 21 years were seropositive for *Cryptosporidium* antibodies, compared with >80% of children aged 6 months to 13 years who resided near the U.S.–Mexican border and were seeking well-child care.[13,14] The incidence of reported cryptosporidiosis in the United States has dramatically increased since 2004, peaking at 4 cases per 100,000 people in 2007.[15] National cryptosporidiosis data from 1995 to 2012 demonstrated that there was a clear increase in cases reported during the period from 2005 to 2008, which persisted during the period from 2009 to 2012. Across all time periods, the highest rates were in children from birth to age 14 years, and cases were most frequently reported in children aged 1 to 4 years.[16] However, compared with earlier years, the rates in children decreased from 2009 through 2012.[17]

Transmission of *Cryptosporidium* occurs throughout the United States, with increased reporting in Midwestern states.[15,16] However, cryptosporidiosis is a highly underdiagnosed and underreported diarrheal illness. Infected patients can be asymptomatic, those with symptoms might not seek health care, health care providers might not request laboratory diagnostics when evaluating non-bloody diarrhea, requested ova and parasite testing might not include *Cryptosporidium* testing, and positive laboratory results are not always reported to public health officials.[16]

Before effective antiretroviral therapy (ART) became available, most patients with HIV diagnosed with cryptosporidiosis had advanced disease or AIDS. The incidence of cryptosporidiosis in people with HIV has declined dramatically since the introduction of ART.[18-20] During the pre-ART era, the rate of cryptosporidiosis was 0.6 cases per 100 patient-years in children followed in 13 Pediatric AIDS Clinical Trial Group (PACTG) trials (median age of 5.9 years and median CD4 count of 51/mm$^3$).[21] Data from the Perinatal AIDS Collaborative Transmission Study indicate that the rate of chronic intestinal cryptosporidiosis decreased from 0.2 cases per 100 person-years in the pre-ART era to 0.0 cases per 100 person-years in the post-ART era.[22] PACTG data estimated that the mortality rate in children with HIV infection significantly decreased from 7.2 to 0.8 per 100 person-years between 1994 and 2000 and subsequently stabilized through 2006.[23] The proportion of deaths due to all opportunistic infections decreased between 1994 and 2006, with declines most notable in deaths associated with *Cryptosporidium* and *Mycobacterium avium* complex (MAC). A recent prospective, comparative cross-sectional study of ART-treated versus ART-naive pediatric patients with HIV infection in Ethiopia found that *Cryptosporidium* infections were found only in ART-naive patients with low CD4 counts.[24]

## Clinical Manifestations

Symptoms of cryptosporidiosis develop after an incubation period of approximately 1 week (range, 2 to 14 days). Diarrhea—which can be profuse, usually non-bloody, and watery—and weight loss, abdominal pain, anorexia, fatigue, joint pain, headache, fever, and vomiting have been reported in immunocompetent children and adults with *Cryptosporidium* infection.[25] In immunocompetent hosts, illness is self-limiting, and symptoms most often completely resolve within 2 to 3 weeks. Recurrence of symptoms after apparent resolution often has been reported. *Cryptosporidium* infection in children can have a significant impact on nutritional status and growth. A comparison of growth parameters in children with and without *C. parvum* infection in Peru showed that *C. parvum* infection has a lasting adverse effect on linear (height) growth, especially when acquired during infancy.[26] In a cohort of 405 schoolchildren aged 6 to 13 years in Mexico, children with cryptosporidiosis were 2.7 times more likely to be at risk of undernutrition by weight-for-age *z* score and 2.9 times more likely to be at risk of undernutrition by height-for-age *z* score than children without *Cryptosporidium* infection.[27]

Clinical presentation of cryptosporidiosis in patients with HIV infection varies with level of immunosuppression, ranging from no symptoms or transient disease to relapsing, chronic diarrhea or cholera-like diarrhea, which can lead to life-threatening wasting and malabsorption.[28] In immunocompromised children, chronic severe diarrhea can result in malnutrition, failure to thrive, and substantial intestinal fluid losses, resulting in severe dehydration and even death.

Different *Cryptosporidium* spp. and genotypes have been associated with different clinical manifestations. *C. hominis* was associated with vomiting in children without HIV in one study and in children and adults with HIV in a different study, whereas *C. parvum* infection was associated with vomiting in another study in adults with HIV.[29-31] Neither clinical history nor physical examination allows differentiation of cryptosporidial disease from that caused by other pathogens.

Biliary tract disease due to cryptosporidial infection is associated with CD4 counts $\leq 50/mm^3$.[32] Symptoms and signs include fever, right upper abdominal pain, nausea, vomiting, and elevated alkaline phosphatase. Diagnostic studies show dilatation of the common bile duct, thickening of the gall bladder wall, and pericholecystic fluid collection. Pancreatitis is rare. Although cryptosporidial infection usually is limited to the gastrointestinal (GI) tract, respiratory disease has been reported in which no pathogen other than *Cryptosporidium* was detected in sputum.[33,34]

## Diagnosis

Health care providers should specifically request *Cryptosporidium* testing because standard ova and parasite testing may not include *Cryptosporidium* spp. Though not extensively evaluated in children with HIV, diagnostic tests for *Cryptosporidium* are expected to perform similarly as in children without HIV.

Monoclonal antibody-based direct fluorescent assays and antigen-detection assays (such as enzyme-linked immunosorbent assay [EIA]) can be used to diagnose cryptosporidiosis because of their enhanced sensitivity and specificity as compared with microscopy.[35-38] Oocyst excretion can be intermittent; therefore, the parasite might not be detected in every stool, and stool specimens collected on 3 consecutive days should be examined before considering test results to be negative.[39] Some immunochromatography assays have been shown to have poor sensitivity and specificity.[40] With rapid test methods, confirmation by microscopy should be considered.

Commercially available multiplex molecular test panels for GI pathogens that include *Cryptosporidium* are now available. When compared with microscopy, the sensitivity for detection of parasitic pathogens was 91.7% for *Cryptosporidium*.[41] In a multicenter evaluation at four geographically distinct clinical sites across the United States, the panel demonstrated a sensitivity of 97.1% and specificity of 98.4% when compared with conventional PCR.[42] This methodology is becoming the new standard of care as it becomes more widely available.

Molecular characterization tools are being increasingly used to differentiate *Cryptosporidium* species in outbreak investigations and infection/contamination source tracking. *Cryptosporidium* isolates cannot be reliably genotyped or subtyped if stool is preserved in formalin, sodium acetate-acetic acid-formalin (SAF), or low-viscosity polyvinyl alcohol (LV-PVA).

## Prevention Recommendations

### *Preventing Exposure*

Caregivers and children with HIV infection should be educated and counseled about the different ways *Cryptosporidium* can be transmitted. Modes of transmission include having direct contact with fecal material from individuals with *Cryptosporidium* infection (particularly children's diapers) and from infected young animals, swallowing or drinking contaminated water, including during recreational activities, and eating contaminated food. Maternal infection with *Cryptosporidium* has been associated with infection in young infants demonstrating the importance of caregiver hygiene.[43]

Hand washing is probably the most important step to reduce the risk of *Cryptosporidium* infection. Children with HIV infection should always wash their hands before preparing or eating food; after using the toilet;

after contact with children in diapers; after contact with clothing, bedding, toilets, or diapers soiled by anyone who has diarrhea; after touching pets or other animals; and after touching anything that might have come in contact with even the smallest amounts of human or animal feces (such as sand in a sandbox).

Children with HIV infection should avoid contact with pre-weaned bovine calves, other young animals (particularly dogs and cats aged <6 months and lambs and goat kids), ill animals, stray animals, and stool from any animals or humans or surfaces known to be contaminated with animal or human feces.[11] Children with HIV infection should avoid petting zoos and animal areas at farms and camps. However, if a child with HIV does visit an animal habitat, an immunocompetent caregiver should clean the child's shoes and any other surfaces possibly contaminated by feces (such as clothes and stroller wheels).

Children with HIV infection should avoid drinking water directly from ponds, streams, springs, lakes, or rivers, or swallowing water they swim or play in regardless of whether it is chlorinated. Caregivers and children with HIV infection should be aware that recreational water—including lakes, rivers, salt-water beaches, swimming pools, waterparks, hot tubs, spas, water playgrounds, and ornamental water fountains might be contaminated with human or animal feces that contain *Cryptosporidium*.

Some outbreaks of cryptosporidiosis have been linked to ingestion of water from contaminated municipal water supplies; the incidence of these outbreaks has dramatically decreased since the mid-1990s because of improved water treatment targeting the inactivation and removal of *Cryptosporidium*. To decrease the risk of cryptosporidiosis during outbreaks or when otherwise advised by local public health officials to boil water, heat water used for preparing infant formula, drinking, making ice, etc. at a rolling boil for 1 minute. After the boiled water cools, put it in a clean bottle or pitcher with a lid and store it in the refrigerator. Water bottles and ice trays should be cleaned with soap and water before each use. Do not touch the inside of these containers after cleaning. Information on filtering tap water and home water distillers can be found on the Centers for Disease Control and Prevention (CDC) website at Prevention & Control: Immunocompromised Persons.

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

All vegetables or fruit to be eaten uncooked should be thoroughly washed. If extra steps are required to make water safe, this safe water should be used to wash fruits and vegetables. When possible, fruit to be eaten raw should be peeled after washing. Unpasteurized dairy products, including raw milk, should not be consumed. Because cooking food kills *Cryptosporidium*, cooked food and heat-processed foods are generally safe if, after cooking or processing, they are not handled by someone infected with the parasite or exposed to contaminated water.

When traveling internationally, particularly in low-resource settings, people with HIV infection should be warned to avoid drinking tap water and also to not to use it to brush teeth. Ingesting ice made from tap water, raw fruits, and raw vegetables should also be avoided. Steaming-hot foods, self-peeled fruits, bottled and canned processed drinks, and hot coffee or hot tea are generally safe.

In hospitals, standard precautions are recommended. However, if the patient is diapered or incontinent, contact precautions should be used for the duration of illness. In addition, contact precautions may be used to control institutional outbreaks of cryptosporidiosis. Some experts recommend that severely immunocompromised patients with HIV not share a room with a patient with cryptosporidiosis because of the potential for fomite transmission. The potential for respiratory transmission of *Cryptosporidium* has been suggested.[34] However, no specific modifications to current prevention recommendations have been suggested.

Adolescents with HIV infection who are sexually active should be counseled about avoiding sexual practices that could result in oral exposure to feces (such as oral-anal contact). To reduce the risk of exposure to feces, adolescents should use dental dams or similar barrier methods for oral-anal and oral-genital contact, wear latex gloves during digital-anal contact, and change condoms after anal intercourse. Frequent washing of hands and genitals with warm, soapy water during and after sexual activities that could bring these body parts in contact with feces might further reduce the risk of *Cryptosporidium* infection.

Additional information on prevention can be found on CDC's website at Prevention & Control: Immunocompromised Persons.

### *Preventing Disease*

Because chronic *Cryptosporidium* infection occurs most often in patients with HIV with advanced immunodeficiency, ART to prevent or reverse severe immune deficiency is a primary modality for prevention of *Cryptosporidium*-associated disease in children with HIV infection.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

Immune reconstitution resulting from ART often results in clearance of *Cryptosporidium* infection. Effective ART is the primary initial treatment for these infections in children and adults with HIV infection who are not already receiving ART.[19,24,44] *In vitro* and observational studies, some of which are case series, suggest that ART containing a protease inhibitor (PI) might be preferable to other ART regimens because of a direct effect of the PI on the parasite.[44-53] PIs also increase production of interferon-gamma, which in turn inhibits *Cryptosporidium* infection. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Antimotility agents to combat malabsorption of nutrients and drugs should be used with caution.

Other than ART, there is no consistently effective therapy to treat cryptosporidiosis in patients with HIV infection.[54,55] Multiple agents have been investigated in small randomized controlled clinical trials in adults with HIV, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract.[56] Azithromycin and roxithromycin have also been investigated in small open-label studies.[57] No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has yet been shown consistently effective and durable when used alone without concomitant ART.[54,55] The duration of treatment in patients with HIV is also uncertain.

While no agent has consistent, proven efficacy for treating cryptosporidiosis in immunocompromised patients, including patients with HIV, nitazoxanide has been shown to reduce the load of parasites and was associated with clinical improvement in some studies in populations with and without HIV infection.[58] An Egyptian clinical trial in 100 adults and children without HIV infection randomized patients to a 3-day course of nitazoxanide or placebo.[59] Nitazoxanide therapy reduced the duration of both diarrhea and oocyst shedding; in children, clinical response was 88% with nitazoxanide and 38% with placebo. No severe adverse events were reported, and adverse events that were reported were similar in the treatment and placebo groups in this study. A study in Zambia in 100 malnourished children (half of whom had HIV) aged 12 to 35 months reported a clinical response in 56% of children without HIV treated with nitazoxanide and in 23% of those receiving placebo.[60] However, in the children with HIV infection, no benefit from nitazoxanide was observed (clinical response in 8% treated with nitazoxanide and in 25% receiving placebo). In a subsequent study of 60 children with HIV with cryptosporidiosis, the same investigators reported no significant benefit using twice the recommended dose administered for 28 days.[61] It should be noted that the children in the Zambian studies were not receiving ART. In a study in adults with HIV not receiving ART who had CD4 counts >50 cells/mm³, the administration of 14 days of nitazoxanide resulted in a parasitological cure rate of 71% (10 of 14 patients) at a dose of 500 mg twice daily and 90% (9 of 10 patients) at a dose of 1,000 mg twice daily as compared with 20% among placebo recipients.[62] In a cohort of 365 HIV-positive patients aged >3 years with *Cryptosporidium* infection who received nitazoxanide as part of a compassionate use program in the United States, sustained clinical response while on treatment was achieved in 59% of the patients. Clinical response was associated with negative stools ($P < 0.0001$). In this cohort, nitazoxanide was found to be safe at higher doses (up to 3,000 mg/day) and for long durations of treatment.[63]

Given the seriousness of this infection in immunocompromised individuals and the potential benefit suggested in some studies, use of nitazoxanide should be considered in immunocompromised children with HIV infection (in conjunction with ART for immune restoration).[54,55] Given that ART might directly inhibit the parasite, it is possible that the combination of ART and parasitic therapy might be synergistic. Nitazoxanide is approved in the United States to treat diarrhea caused by *Cryptosporidium* and *Giardia lamblia* in immunocompetent children aged ≥1 year and is available in liquid and tablet formulations. The recommended dose for children is 100 mg twice daily for children aged 1 to 3 years and 200 mg twice daily for children aged 4 to 11 years. A tablet preparation (500 mg twice daily) is available for children aged ≥12 years. Nitazoxanide should be administered with food.

Paromomycin, a non-absorbable aminoglycoside indicated for the treatment of intestinal amoebiasis, is not approved for treatment of cryptosporidiosis. Two small, randomized trials evaluating the efficacy of paromomycin for treatment of patients with HIV infection found clinical improvement or reduced oocyst excretion in those treated with paromomycin.[64,65] However, other reports of paromomycin treatment in patients with HIV infection found repeated failure to cure.[66] Therefore, data do not support a recommendation for use of paromomycin for cryptosporidiosis. Clinical or parasitological cure has been documented with use of paromomycin and azithromycin in combination in case series of patients with HIV with cryptosporidial diarrhea and case reports of patients with HIV with pulmonary cryptosporidiosis.[67-69]

### *Monitoring and Adverse Events, Including IRIS*

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte imbalance, malnutrition, and weight loss. In severely ill patients, total parenteral nutrition might be indicated. One case report describes immune reconstitution inflammatory syndrome, specifically terminal ileitis, in association with treatment of cryptosporidiosis.[70]

In general, nitazoxanide is well tolerated and side effects are mild, transient, and generally limited to the GI tract.

### *Managing Treatment Failure*

The most important steps for managing treatment failure are optimizing ART to increase CD4 counts and providing supportive treatment.

### *Preventing Recurrence*

No pharmacologic interventions, other than ART to prevent or reverse severe immune deficiency, are known to be effective in preventing recurrence of cryptosporidiosis. Good hygiene, including frequent handwashing, and avoiding potentially contaminated water and food and high-risk environmental contact can help prevent reinfection.

### *Discontinuing Secondary Prophylaxis*

Not applicable.

## Recommendations

**I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent episodes of cryptosporidiosis?**

- Cryptosporidiosis can be prevented by practicing good hygiene (e.g., frequent handwashing), avoiding drinking water that might be contaminated, avoiding high risk swimming exposures (e.g., drinking swimming water, especially in pools and water playgrounds frequented by very young children), and not eating food that might be contaminated (**expert opinion**).
- Children with HIV infection should avoid contact with pre-weaned bovine calves, lambs, goat kids, ill animals, young dogs and cats, stray animals, and stool from any animals or humans or surfaces known to be contaminated with human or animal feces (**expert opinion**).
- ART for children with HIV infection to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric cryptosporidiosis (**strong, low**).

  A prospective, comparative cross-sectional study of ART-treated versus ART-naive pediatric patients with HIV infection in Ethiopia found that *Cryptosporidium* infections were found only in ART-naive patients with low CD4 counts.[24] A retrospective/prospective cohort study in adults with HIV infection in South Ethiopia demonstrated that patients who initiated ART with a CD4 count of <500/mm$^3$ and received health interventions including provision of household water treatment, safe water storage, soap, and anti-helminthic drugs had decreased rate of cryptosporidiosis, even among patients with CD4 counts <200 cells/ mm$^3$.[71]

**II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat cryptosporidiosis?**

- Treatment with ART is the best intervention in children with HIV infection and cryptosporidiosis (**strong, moderate**).
- Immune reconstitution resulting from ART often results in clearance of Cryptosporidium infection, and ART is the primary initial treatment for these infections in children with HIV infection who are not already receiving ART.[19,24,44]
- Nitazoxanide, in addition to ART, can be considered for cryptosporidiosis in children with HIV (**strong, moderate**).

  A clinical trial comparing nitazoxanide versus placebo in children without HIV infection demonstrated that resolution of diarrhea and parasitologic cure were significantly higher in children treated with nitazoxanide.[59] In a prospective cohort of patients with HIV infection with cryptosporidiosis treated with nitazoxanide, sustained clinical response was achieved in 59% of patients, and 57% of patients had *Cryptosporidium*-negative stool before completing the study.[63] However, a study of malnourished Zambian children demonstrated no benefit from nitazoxanide among children with HIV (clinical response in 8% treated with nitazoxanide and in 25% receiving placebo) but did show benefit when both children with and without HIV infection were included.[60]
- Dehydration and electrolyte abnormalities should be corrected, and nutritional support should be provided as appropriate (**expert opinion**).

  There are no studies that address this specific management issue in cryptosporidiosis. However, recognition and management of hydration status, electrolyte imbalance, and nutritional needs are key to management of infectious diarrhea.

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# Cytomegalovirus

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| Panel's Recommendations |
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| I. Is there an indication for cytomegalovirus (CMV) antibody testing in children with asymptomatic HIV (versus not testing) to guide clinical management?<br>• 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/mm$^3$ or CD4 percentage <10%) (**strong, low**).<br>II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not screening)?<br>• 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.<br>III. Is primary prophylaxis against CMV recommended for children with HIV who are CMV-seropositive (versus not providing prophylaxis)?<br>• 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/mm$^3$ in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years (**strong, moderate**).<br>• Prophylaxis with valganciclovir may be appropriate for CMV-seropositive children with HIV who are severely immunosuppressed (i.e., CD4 count <50 cells/mm$^3$ in children aged ≥6 years, or CD4 percentage <5% in children aged <6 years) (**weak, low**).<br>• Cessation of primary prophylaxis can be considered when the CD4 count is sustained at >100 cells/mm$^3$ for children ≥6 years of age, or CD4 percentage >10% in children <6 years (**weak, low**).<br>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)?<br>• Children with HIV aged <5 years who are CMV infected and severely immunosuppressed (i.e., CD4 count <50 cells/mm$^3$ 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.<br>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?<br>• 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**).<br>• Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV (**strong, moderate**).<br>• 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**). |

| Panel's Recommendations |
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| Combination treatment with IV ganciclovir and foscarnet may also be preferable as initial therapy to stabilize CMV neurologic disease and maximize response (**weak, very low**).<br>• In children with HIV and symptomatic congenital CMV infection, treatment with valganciclovir (or IV ganciclovir) for 6 months is recommended provided it can be started during the first month of life (**strong, moderate**). This recommendation is based on studies among children with symptomatic congenital CMV infection but without HIV.<br><br>**VI. Is secondary prophylaxis after treatment of CMV disease (versus no secondary prophylaxis) recommended in severely immunocompromised children with HIV?**<br>• 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**).<br>• 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.<br><br>**VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children with HIV who have well-controlled HIV (versus continuation of secondary prophylaxis)?**<br>• 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/mm$^3$ for children aged ≥6 years (**weak, low**).<br>• 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**).<br>• 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/mm$^3$ in those aged ≥6 years (**strong, moderate**). |
| *Rating System*<br>*Strength of Recommendation: Strong or Weak*<br>*Quality of Evidence: High, Moderate, Low, or Very Low* |

## Epidemiology

Infection with human cytomegalovirus (CMV) is common and usually not apparent; CMV can be acquired *in utero* or during infancy, early childhood, or adolescence.[1] Transmission can occur vertically from a pregnant person with CMV to their offspring; horizontally by contact with virus-containing breast milk, saliva, urine, or genital fluids; through transfusion of infected blood; or through transplantation of infected organs. During infancy and early childhood, infection usually occurs during breastfeeding by mothers with CMV infection or from exposure to household members with CMV, particularly siblings, who are shedding virus asymptomatically from saliva or urine. CMV infection is more apt to occur at younger ages when sanitary conditions are suboptimal. Among adolescents, sexual transmission is the major mode of CMV acquisition.

Age-related prevalence of CMV infection varies widely depending on living circumstances and social customs. Breastfeeding, child-rearing practices, crowding, sanitation, and sexual behavior most likely influence age-related variations in CMV prevalence. Where rates of maternal seropositivity are high and breastfeeding is common, more than half of infants acquire CMV during the first year of life.[2-4] Group care of children facilitates spread of CMV, especially in toddlers, and leads to higher prevalence of infection in children who attend childcare centers and in their caregivers.[5-8] Toddlers with CMV infection may shed CMV for many months after primary infection, which also poses a transmission risk for CMV-susceptible daycare workers.[6,9-11] In Africa, Asia, and Latin America, most children are infected with CMV before adolescence. In the United States and Western Europe, the prevalence of antibody to CMV in adults from middle and upper socioeconomic strata is 40% to 60%, whereas the prevalence in adults with low income is ≥80%.[12,13] Overall, among U.S. women of childbearing age, the prevalence of CMV infection is 30% to 70%, with the highest prevalence in women in lower socioeconomic strata.[14] The prevalence of CMV infection among pregnant women with HIV is higher than in the general population, with approximately 90% of pregnant women with HIV coinfected with CMV.[15,16]

CMV is the most common congenitally acquired infection, with prevalence estimates in live-born infants ranging from 0.3% to 1.3%.[17] Congenital (*in utero*) CMV infection may occur in infants born to women who have primary or non-primary CMV infection during pregnancy.[18-20] Following primary infection during pregnancy, the rate of transmission to the fetus is approximately 30% to 40%.[21,22] According to currently available diagnostic methodologies, the exact rate of transmission in non-primary maternal infections remains largely unknown and difficult to determine. Data from published cohorts and meta-analyses indicate that rates of non-primary congenital CMV (cCMV) transmission are substantially lower than for primary infection.[23-26]

Non-primary maternal infection can result in congenital infection because of reactivation of latent infection or reinfection with a different CMV strain in CMV-seropositive women during pregnancy.[18,27-30]

CMV also can be transmitted from mother to infant during the intrapartum or postpartum periods via infected maternal secretions or breast milk. Symptomatic CMV disease due to postnatal acquisition can occur in premature neonates. Long-term sequelae are rare in premature or term infants who acquire CMV perinatally or postnatally.[31-35]

Among CMV-seropositive women, the rate of CMV shedding from the cervix is higher in women with HIV coinfection than in women without HIV (52% and 6% to 21% respectively, by polymerase chain reaction [PCR]).[36] In the era before antiretroviral therapy (ART), the overall rate of cCMV infection among infants born to mothers with HIV was 4.45% and was similar for infants with HIV and those without HIV (4.3% among infants with perinatal HIV and 4.5% among those without HIV).[37] However, more recent studies from South Africa of pregnant women with HIV who are not on ART have reported prevalence rates ranging from 3.8% to 6.5% among infants exposed to HIV, with a sixfold higher cCMV rate in infants with *in utero* HIV transmission.[38,39] In the ART era, prevalence of cCMV infection in infants born to mothers with HIV has ranged from 2.2% to 5.2%.[15,40-44] From 1988 to 2004 (years encompassing both the pre-ART and ART eras), the rates of cCMV infection in infants born to mothers with HIV were 10.3% to 21% for the infants with HIV and 2.2% to 3.8% for those without HIV.[40,45] In two studies, rates of *in utero* HIV transmission to neonates born to women with HIV were higher among infants with cCMV infection (67% to 70%) than among those without cCMV infection (36% to 42%), suggesting that the rate of intrauterine viral co-transmission of HIV and CMV is high.[40,46] More recent published data from a high–HIV prevalence area in the ART era confirmed that *in utero* HIV transmission is significantly higher in neonates who are HIV exposed with cCMV compared to those without cCMV infection (odds ratio 20.1, 95% CI, 6.09–66.46).[44] In neonates with cCMV infection, the percentage of infants with symptomatic cCMV infections was 23.1% among those coinfected with HIV-1, compared with 6.7% among those without HIV-1.[40] These data indicate that the prevalence of cCMV may be higher among infants exposed to HIV compared with those unexposed to HIV, and that rates of cCMV and HIV co-transmission as well as symptomatic cCMV infection are high among infants exposed to HIV.

The risk of acquiring CMV infection during early childhood appears to be greater for children with HIV than for children without HIV (39.9% vs. 15.3%).[37] The rate of CMV acquisition in children with HIV appears to be particularly high during the first 12 months of life (35% to 42%) and, through age 4 years, remains higher for those with HIV than for those without HIV.[4,37,46-49] In the pre-ART era, children with HIV/CMV coinfection were more likely to have HIV disease progression than children with HIV mono-infection, but in the ART era, HIV/CMV coinfection has not been associated with excess mortality.[37,48]

CMV disease occurs less frequently among children with HIV than among adults with HIV, but still contributed substantially to morbidity and mortality among children with HIV in the era before ART. In the pre-ART era, CMV caused 8% to 10% of pediatric AIDS-defining illnesses.[50] Data in adults with HIV have shown a 75% to 80% decrease in the incidence of new cases of CMV end-organ disease with the advent of ART, with an incidence estimated to be <6 cases per 100 person-years.[51] In a study of opportunistic infections in approximately 3,000 children followed in Pediatric AIDS Clinical Trials Group studies during the pre-ART era, the frequency of CMV retinitis was 0.5 cases per 100 child-years and, of other CMV disease, 0.2 cases per 100 child-years.[52] The rate varied significantly by CD4 T lymphocyte (CD4) cell percentage; the incidence of CMV retinitis was 1.1 cases per 100 child-years in children with CD4 percentage <15% and 0.1 case per 100 child-years in children with CD4 percentage >25%. In the same cohort during the ART era, the overall rate of CMV retinitis was <0.5 per 100 child-years.[53] In the Perinatal AIDS Collaborative Transmission Study, the incidence of non-ocular CMV disease before and after January 1997 (during pre-ART and ART eras) was 1.4 per 100 child-years and 0.1 per 100 child-years, respectively, and CMV retinitis declined from 0.7 to 0.0 per 100 child-years.[54]

Children with symptomatic HIV who are coinfected with CMV have a higher rate of CMV viruria than do children who have asymptomatic HIV or are HIV exposed.[55] Overall, up to 60% of children with AIDS shed CMV. This compares with one-third of all children with HIV; 15% to 20% of children with CMV infection who are HIV exposed but uninfected; and <15% of infants with CMV infection who are not exposed to HIV.[56] Similarly, in older children and adolescents with perinatally acquired HIV who are on ART or ART-naive, the frequency of CMV DNAemia was higher compared to HIV-uninfected controls and was associated with impaired growth and poor lung function.[57]

## Clinical Manifestations

In the general population, approximately 10% of infants with cCMV infection are symptomatic at birth. The rate of symptomatic infection among infants with congenitally acquired CMV is higher in infants with HIV (23.1%) than in children who are HIV exposed but uninfected (6.7%), even in the ART era.[40] In studies of cohorts of neonates without HIV with symptomatic cCMV disease, clinical presentations commonly observed included size that was small for gestational age, petechiae, jaundice, hepatosplenomegaly, chorioretinitis, microcephaly, intracranial calcifications, and sensorineural hearing loss (SNHL).[58,59] Mortality of children with symptomatic cCMV disease is as high as 30%. Approximately 40% to 58% (and in specific cohorts, as many as 90%) of infants with symptomatic CMV disease at birth who survive have late complications, including substantial hearing loss, intellectual and developmental disabilities, chorioretinitis, optic atrophy, seizures, or learning disabilities.[17,60] Although most children with cCMV infection do not have symptoms at birth, 10% to 15% of children with asymptomatic cCMV infection are at risk of later developmental abnormalities, SNHL, chorioretinitis, or neurologic deficits. Infants with asymptomatic cCMV infection may have early or late-onset SNHL as the only manifestation of congenital infection. Rates of hearing loss and other late complications of cCMV infection among infants with vertically transmitted, asymptomatic, HIV/CMV coinfection are unknown. Premature neonates who acquire CMV postnatally can be asymptomatic or can have evidence of disease, such as hepatitis, thrombocytopenia, or pneumonitis.

Among children with HIV, HIV disease seems to progress more quickly in those coinfected with CMV than in those without CMV infection.[37,45,50,55] In one study from the pre-ART era, 53% of infants coinfected with HIV and CMV had progression to AIDS or had died by age 18 months, compared with 22% of children with HIV without CMV infection; those with HIV/CMV coinfection also were more likely to have central nervous system (CNS) manifestations (36% versus 9%). The relative risk of HIV disease progression in children coinfected with CMV compared with children without CMV was 2.6 (95% CI, 1.1–6.0).[37] Limited data indicate that infants with HIV/CMV coinfection treated with ART do not experience accelerated HIV disease progression.[61,62]

CMV retinitis is the most frequent severe manifestation of CMV disease among children with HIV, accounting for approximately 25% of CMV AIDS-defining illnesses in the pre-ART era. CMV retinitis among young children with HIV is frequently asymptomatic and discovered on routine eye examination.[63] Older children with CMV retinitis present similarly to adults, with floaters, loss of peripheral vision, or reduction in central vision. Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates and associated retinal hemorrhages. A more indolent, granular retinitis also can occur. Children with HIV with CD4 counts <100 cells/mm$^3$ are more likely than those with higher CD4 counts to develop CMV retinitis; however, CD4 count is less predictive of risk of CMV disease in young infants, and systemic and localized CMV disease can occur in infants with HIV with higher, age-adjusted CD4 counts.[56,64] The rate of CMV retinitis in children with HIV has decreased in the ART era, with reported rates of 0.0% to 0.4%. [53,65,66]

End-organ CMV disease has been reported in the lung, liver, gastrointestinal (GI) tract, pancreas, kidney, sinuses, and CNS of children with HIV, but is rare in the era of ART.[64,67-69] In children with HIV who have extraocular CMV disease, predominantly nonspecific symptoms (e.g., fever, poor weight gain, and loss of developmental milestones, with laboratory abnormalities of anemia, thrombocytopenia, and elevated lactic dehydrogenase) are initially observed, although the extent to which CMV or HIV themselves contribute to these findings is unclear.[56] Gastrointestinal (GI) manifestations among children with HIV include CMV colitis (the most common GI manifestation), oral and esophageal ulcers, hepatitis, ascending cholangiopathy, or gastritis. Odynophagia is a common presentation of CMV esophagitis, whereas abdominal pain and hematochezia frequently occur with CMV colitis. Sigmoidoscopy in CMV colitis is nonspecific, demonstrating diffuse erythema, submucosal hemorrhage, and diffuse mucosal ulcerations. Esophageal or colonic ulcerations may cause perforation or hemorrhage.

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

CNS manifestations of CMV include subacute encephalopathy, myelitis, and polyradiculopathy (primarily observed in adults but rarely reported in children). The subacute or chronic encephalopathy of CMV can be difficult to differentiate clinically from HIV dementia, with symptoms of confusion and disorientation attributable to cortical involvement. Focal signs can be attributed to lesions in the brainstem. Cerebrospinal fluid (CSF) findings are nonspecific and may include leukocytosis with polymorphonuclear predominance (>50% of patients), elevated protein (75% of patients), and low glucose (30% of patients). However, up to 20% of children with CMV CNS involvement have completely normal CSF indices. CMV also can cause a rapidly progressive, often fatal CNS disease with cranial nerve deficits, nystagmus, and increasing ventricular size.[70]

## Diagnosis

Because CMV is a persistent infection and may reactivate asymptomatically during inflammatory states, CMV disease is diagnosed by a combination of consistent clinical manifestations with supportive virologic testing indicative of CMV infection. A positive CMV immunoglobulin G (IgG) antibody assay in an infant aged <12 months can reflect transplacental maternal antibody transfer and may not indicate infection of the infant. In older children, a positive CMV IgG antibody assay indicates CMV infection. In children of any age, a positive CMV culture or PCR assay confirms CMV infection.

CMV can be isolated in cell culture from peripheral blood leukocytes, body fluids (e.g., urine, saliva), or tissues. A positive blood buffy-coat culture establishes CMV infection and increases the likelihood that disease or symptoms are caused by CMV because children with CMV-positive blood cultures are at higher risk of end-organ disease. Recovery of virus from tissues (e.g., with endoscopically guided biopsies of GI or pulmonary tissue) with supportive histopathology provides evidence of disease causation in symptomatic patients. The limitation of cell culture is that detection of visible cytopathic effects in cell culture takes 1 to 6 weeks. Staining of shell vial culture with CMV monoclonal antibodies or tissue immunostaining for CMV antigens can allow earlier diagnosis of infection.[71,72] Using centrifugation-assisted shell vial culture amplification techniques, CMV can be detected within 16 to 40 hours of culture inoculation. Histopathology demonstrates characteristic "owl's eye" intranuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens. Staining with monoclonal antibodies for CMV antigens also can be done on cells obtained from bronchoalveolar lavage.

Several methods have been used to detect CMV antigen or DNA directly and identify patients at risk of CMV disease; these methods include detection of pp65 antigenemia, qualitative and quantitative PCR, and DNA hybridization. The DNA assays are more sensitive than buffy coat or urine cultures for detecting CMV and can be used to identify patients at higher risk of clinically recognizable disease. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV CNS disease. Quantitative DNA PCR can be used as a marker for risk of disease and to monitor response to therapy.[73] The National Institute of Standards and Technology and the World Health Organization Expert Committee on Biological Standardization have developed reference standards for nucleic acid–based assays for CMV DNA, permitting comparison of quantitative DNA PCR test results among clinical laboratories.[74,75]

To diagnose cCMV infection, the traditional gold standard is a positive viral culture from saliva or urine collected within the first 21 days of life. More recently, saliva and urine PCR (but not blood PCR) also have been validated to diagnose cCMV infection.[76,77] Beyond 21 days of age, positive cultures and PCR tests can be due to postnatally acquired CMV infection.

To diagnose acquired CMV disease, culture, antigenemia, and PCR can be used to provide supportive laboratory evidence for clinically suspected CMV disease. However, these tests may be positive in the absence of clinical disease and therefore do not diagnose CMV disease in the absence of clinical findings. Alternatively, localized CMV disease (e.g., GI disease) may not be accompanied by positive culture or PCR of blood, and diagnosis may require direct sampling of the involved organ for CMV testing.

## Prevention Recommendations

### *Preventing Exposure*

Although breastfeeding can result in breastmilk-associated CMV transmission to infants, maternal CMV infection is not a contraindication to breastfeeding.[3,78,79]

Infants who were exposed to HIV but are uninfected and children, adolescents, and adults with HIV who are seronegative for CMV and require blood transfusion should be administered only CMV antibody–negative or leukocyte-reduced cellular blood products in nonemergency situations.

Adults and adolescents with HIV who are childcare providers or parents of children in childcare facilities should be informed that they are at increased risk of CMV infection. Risk of CMV infection can be diminished by optimal hygienic practices (e.g., handwashing). Adolescents are at risk of CMV acquisition through oral–oral contact (kissing) and genital–genital contact; the latter risk may be decreased with condom use.

### *Preventing First Episode of Disease*

The primary methods of preventing severe CMV disease in children with HIV are prevention of severe immunosuppression by treating with ART and recognition of the early manifestations of disease. CMV antibody testing is recommended at age 1 year (or at baseline evaluation for children >1 year of age) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 count <100 cells/mm$^3$ or CD4 percentage <10%). Children with HIV aged <5 years who have CMV and are severely immunosuppressed (i.e., CD4 count <50 cells/mm$^3$ or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months. Older children should be counseled to report floaters in the eye and visual changes immediately, as recommended for adults with HIV.[80]

Since the advent of ART, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents in people coinfected with CMV and HIV is not recommended.[54] CMV end-organ disease is best prevented by ART to maintain a CD4 count >100 cells/mm$^3$ (CD4 percentage >10% in children <6 years). If this is not possible, prophylaxis with valganciclovir can be considered for children and adolescents with HIV who are CMV-seropositive and who have severe immunosuppression, defined as CD4 counts of <50 cells/mm$^3$ for children age ≥6 years or as a CD4 percentage <5% for children age <6 years. However, data supporting the efficacy of antiviral prophylaxis against CMV in pediatric patients with HIV are lacking, and CMV disease has been observed in children with higher CD4 counts than the thresholds suggested for primary prophylaxis.[52,81] Randomized clinical trials of ganciclovir prophylaxis in adult patients with AIDS and low CD4 counts produced conflicting results, with one trial showing a 49% reduced risk of CMV disease and the other trial showing no benefit.[82-84] Ganciclovir is associated with hematologic toxicity, and animal studies indicate teratogenicity and carcinogenicity. Therefore, ART remains the preferred approach to prevent CMV disease in children with HIV.

In a retrospective cohort study in adults with HIV with CD4 counts <100 cells/mm$^3$ and CMV viremia who did and did not receive preemptive treatment with antiviral therapy (ganciclovir, valganciclovir, or foscarnet), preemptive CMV therapy resulted in a 25% decreased incidence of CMV end-organ disease.[85] The use of CMV preemptive therapy has not been studied in pediatric patients with HIV.

The rate of CMV and HIV co-transmission *in utero* is higher than the rate of cCMV infection in newborns who do not have HIV.[40,44,45,48] Therefore, testing for cCMV infection in infants known to have vertically transmitted HIV is recommended in the first 21 days of life. Some experts also recommend testing all infants born to mothers with HIV for cCMV, because of the increased risk of HIV/CMV co-transmission and the narrow postnatal window (21 days) during which the diagnosis of cCMV infection can be made. Asymptomatic cCMV infection is associated with late-onset hearing loss in children without HIV.[59] Based on experience in infants without HIV, serial evaluation for hearing loss (e.g., at 3 to 6 month intervals for the first year, then every 6 to 9 months until 3 years of age, then annually at least until 6 years of age) should be considered for infants with cCMV infection (symptomatic and asymptomatic).[86]

### *Discontinuing Primary Prophylaxis*

Because primary prophylaxis with antiviral agents in individuals coinfected with CMV and HIV usually is not recommended (as discussed above), consideration for discontinuing primary prophylaxis usually is unnecessary. When valganciclovir primary prophylaxis is provided, cessation of prophylactic treatment can be considered when the CD4 count is sustained at >100 cells/mm$^3$ in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years.

## Treatment Recommendations

### *Treating Disease*

#### **Congenital CMV Infection**

Treatment of newborns who have symptomatic cCMV disease involving the CNS with intravenous (IV) ganciclovir for 6 weeks has been evaluated in a series of clinical trials conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group.[87,88] All infants in these studies did not have HIV. In a Phase 3 randomized controlled trial, infants with CNS disease due to cCMV infection who received IV ganciclovir for 6 weeks were less likely to have hearing deterioration over the first 2 years of life and had fewer neurodevelopmental delays at 1 year of life than infants receiving no antiviral therapy.[88,89] However, approximately two-thirds of the infants developed substantial neutropenia during therapy.[88] A subsequent trial comparing 6 weeks to 6 months of oral valganciclovir treatment in infants with symptomatic cCMV infection showed no difference in the primary endpoint of best-ear hearing at 6 months, but showed modest benefit of 6-month valganciclovir therapy for hearing and developmental secondary endpoints at 12 and 24 months in adjusted analysis. The rate of neutropenia observed in valganciclovir-treated infants was lower than previously observed in ganciclovir-treated infants.[90] Consensus recommendations have been published for prevention, diagnosis, and treatment of cCMV infection in pregnant people and neonates.[91]

Based on these results in infants without HIV, oral valganciclovir therapy for 6 months is recommended for infants who are exposed to or have HIV and who have symptomatic cCMV disease, if valganciclovir can be initiated within the first month of life. Neonates with symptomatic cCMV disease can be referred to a pediatric infectious diseases specialist for consideration of valganciclovir therapy and long-term monitoring for sequelae.[88,91,92]

CMV retinitis should be managed in collaboration with an experienced ophthalmologist, and CMV treatment should be instituted in addition to ART. IV ganciclovir, oral valganciclovir, IV foscarnet, and IV cidofovir are all effective treatments for CMV retinitis in adults with HIV.[93-100] For infants and children with HIV, IV ganciclovir is the drug of choice for initial treatment (induction therapy) for acquired CMV disease, including CMV retinitis and other end-organ disseminated CMV disease (e.g., colitis, esophagitis, CNS disease). Oral valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for adults with HIV who have CMV retinitis[95] and is an option in both older children and patients with HIV who have mild CMV disease. The drug is well absorbed from the GI tract and rapidly metabolized to ganciclovir in the intestine and liver. Valganciclovir oral solution has not been studied in pediatric patients for treatment of CMV retinitis but can be considered for transitioning from IV ganciclovir to oral valganciclovir to complete treatment and/or for secondary prophylaxis once improvement in retinitis is noted.

An alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV is foscarnet. Foscarnet used as CMV-suppressive therapy has been associated with increased length of survival relative to ganciclovir in adults with HIV. Doses should be modified in patients with renal insufficiency. Cidofovir is effective in treating CMV retinitis in adults who are intolerant of other therapies. Cidofovir has not been studied in children with CMV disease but can be considered when other options cannot be used.

Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails[101,102] and can be used as initial therapy in children with sight-threatening disease. Combination therapy also has been used for adults with retinitis that has relapsed on single-agent therapy. However, adverse effects, such as hematologic and renal toxicity, can be associated with combination therapy.

Intravitreous injections of ganciclovir, foscarnet, or cidofovir have been used to control retinitis, but biweekly intraocular injections are required. Data in children are limited, and biweekly injections are impractical in most children. Implantation of an intravitreous ganciclovir medication-release device in the posterior chamber of the eye also has been used in adults and adolescents with HIV; however, this device is no longer commercially available. In adults, the combination of oral ganciclovir with a ganciclovir sustained-release intraocular implant, replaced every 6 to 9 months, was superior to daily IV ganciclovir in preventing relapse of retinitis.[103] Among adults with HIV who have sight-threatening CMV lesions adjacent to the optic nerve or fovea, initial treatment with intraocular ganciclovir implant (no longer manufactured) plus IV ganciclovir or oral valganciclovir was preferred by some adult HIV specialists.[93-97] Use of systemic therapy in addition to intraocular ganciclovir has the additional benefit of reducing development of retinitis in the contralateral eye. In adults, small peripheral lesions can be treated with systemic therapy without local treatment. Use of intraocular cidofovir in children is not recommended because of lack of pediatric use data and the risk of ocular hypotony in adults.[104]

### Other CMV Disease Entities

For acquired CMV neurologic disease, prompt initiation of CMV therapy is critical for an optimal clinical response, as well as ART to enable immune reconstitution. Levels of ganciclovir in the CSF are 24% to 70% of plasma levels, and levels in the brain are approximately 38% of plasma levels.[105] Foscarnet concentrations in the CSF are about two-thirds of those in serum.[106] Combination treatment with ganciclovir and foscarnet may be preferable as initial therapy to stabilize disease and maximize response.[64,107] However, this approach may be associated with adverse effects (renal, gastrointestinal, or hematopoietic systems), and the optimal treatment for neurologic disease in children receiving optimized ART is unknown.

Patients with AIDS and recipients of solid organ transplants who have GI disease attributed to CMV appear to benefit from ganciclovir therapy.[108,109] Limited data and data from uncontrolled studies suggest that ganciclovir therapy is useful in patients with AIDS and CMV pneumonia.[110] As with other CMV disease, antiviral management for CMV disease of the GI tract or lungs should also include ART.

## *Monitoring Response to Therapy and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

CMV retinitis should be managed in concert with an experienced ophthalmologist. Recommendations for adults with HIV include indirect ophthalmoscopy of both eyes through a dilated examination of the retina performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment.[80] By extrapolation, similar recommendations are made for children with HIV who have CMV retinitis. Monthly fundus photographs using a standardized photographic technique that documents the appearance of the retina provide the optimum method for following patients and detecting early relapse. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months. However, because relapse of retinitis can occur in patients with immune recovery, regular ophthalmologic follow-up still is needed.

The major side effects of ganciclovir and valganciclovir are myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia) and renal toxicity. Dosing in patients with renal dysfunction should be adjusted according to the measured or estimated creatinine clearance. Dose reduction or interruption because of hematologic toxicity may be necessary in up to 40% of patients receiving IV ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate neutropenia. The main toxicities of foscarnet are decreased renal function and metabolic derangements. Renal toxicity and foscarnet binding to divalent metal ions, such as calcium, led to metabolic abnormalities in approximately one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur. Nephrotoxicity can be reduced with pre-hydration, and metabolic disturbances can be minimized if foscarnet is administered by slow rates of infusion not exceeding 1 mg/kg/minute and by monitoring serum electrolytes to guide electrolyte replacement.[111-113] Concomitant use of other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscarnet therapy. For patients receiving ganciclovir, valganciclovir, or foscarnet, complete blood counts, serum electrolytes, and renal function should be monitored twice weekly during induction therapy and once weekly thereafter.

The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction, including proteinuria, glycosuria, Fanconi syndrome, and acute renal failure. To minimize nephrotoxicity, probenecid should be administered before each infusion, and IV hydration with normal saline should be administered before and after each cidofovir infusion.[114] For patients receiving IV cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while the drug is administered systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases ≥0.5 mg/dL above baseline.

Immune recovery uveitis after initiation of effective ART is an immunologic reaction to CMV that is associated with inflammation in the anterior chamber and/or the vitreous and, therefore, is a form of immune reconstitution inflammatory syndrome (IRIS).[115] Ocular complications of uveitis include macular edema and development of epiretinal membranes, which can cause loss of vision. Patients with low CD4 counts who are starting ART are at risk of IRIS. Frequent ophthalmologic examinations are warranted during the period of immune reconstitution in children who are unable to report symptoms, and ophthalmologic examination is indicated for children of any age who develop visual symptoms. Immune recovery uveitis may respond to periocular corticosteroids or a short course of systemic steroids. Oral valganciclovir was beneficial in one small uncontrolled study.[116]

## *Managing Treatment Failure*

CMV resistance to ganciclovir and valganciclovir can be conferred by mutations in the viral phosphotransferase gene, UL97, or the viral DNA polymerase gene, UL54.[117,118] Resistance to foscarnet or cidofovir occurs because of mutations in the UL54 DNA polymerase gene.[119,120] Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occurs despite ganciclovir therapy. Viral culture and phenotypic antiviral drug susceptibility testing are not generally available in clinical laboratories, but sequencing of the CMV UL97 and UL54 genes from PCR-amplified specimens may be performed in commercial laboratories. Results of genotypic resistance testing have been shown to correlate with clinical outcome of ganciclovir treatment in patients with HIV who have CMV retinitis.[121] Foscarnet is the empiric drug of choice when ganciclovir resistance is suspected.

In patients with CMV retinitis, although drug resistance can occur in patients receiving long-term CMV therapy, early relapse may be caused by the limited intraocular penetration of systemically administered drugs. In adults with HIV whose retinitis has relapsed during systemic treatment, placement of a ganciclovir implant was recommended because it achieved higher drug levels in the eye and often would control the retinitis for 6 to 8 months until the implant required replacement; however, the ganciclovir implant is no longer available from the manufacturer.[122,123] Early first relapse of retinitis should generally be treated with reinduction with the same drug used for initial treatment, followed by reinstitution of maintenance therapy. However, if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent, changing to an alternative drug is reasonable. Combination ganciclovir and foscarnet can be considered, but the combination is associated with greater toxicity.

## *Preventing Recurrence*

Courses of antiviral agents (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) do not cure CMV infection in any host. For most forms of CMV disease in the context of HIV, after induction therapy, patients are given secondary prophylaxis (chronic maintenance therapy) until reconstitution of the immune system or for the remainder of their lives in the absence of immune reconstitution. Regimens that can be considered for chronic maintenance therapy in adults and adolescents include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir; these regimens also are recommended for children.[103,124-130] Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir reportedly are effective for secondary prophylaxis of CMV retinitis,[131,132] although intraocular therapy alone does not protect the contralateral eye or other organ systems and therefore typically is combined with systemic treatment.[103] Frequent intravitreous injections also are impractical in most children.

Chronic maintenance regimens for patients treated for CMV disease should be chosen in consultation with relevant specialists. Chronic maintenance therapy is not routinely recommended for GI disease but should be considered if relapses occur. A role for maintenance therapy for CMV pneumonitis has not been established. For patients with retinitis, decisions should be made in consultation with an ophthalmologist, considering the anatomic location of the retinal lesion, vision in the contralateral eye, and patients' immunologic and virologic status.

## *Discontinuing Secondary Prophylaxis*

Multiple case series have reported that maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose CD4 counts have increased substantially in response to ART.[133-139] These patients have remained disease free for >30 and up to 95 weeks of follow-up. Plasma HIV RNA levels varied among the patients in these studies, supporting the hypothesis that the CD4 count is the primary determinant of recovery of the immune response. However, CMV retinitis can occur in ART-treated adults with high CD4 counts,[140] suggesting that CMV-specific cellular immunity may be important in controlling CMV in adults with HIV with immune reconstitution[141,142] and reinforcing the importance of ongoing monitoring. In adults with HIV with CMV retinitis, discontinuation of secondary prophylaxis can be considered for patients whose lesions have been treated for at least 3 to 6 months and are inactive and who have sustained (i.e., 3–6 months) increases in CD4 cell counts to >100 cells/mm$^3$ in response to ART.[80]

The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children with HIV has not been as well studied. Low or undetectable HIV replication in children is the strongest correlate with CMV immune reconstitution and a higher frequency of CMV-specific CD4 cells.[143] Early institution of ART may help control CMV infection in children with HIV by maintaining or restoring normal CD4 count and cytotoxic T-lymphocyte responses.[144] Significant toxicities associated with antiviral drugs, including those identified in *in vitro* and animal models, must be considered when deciding whether to discontinue secondary prophylaxis.

Recognizing the limitations of the data in children but drawing on the experience in adults, discontinuing prophylaxis can be considered in children who are receiving ART and have a sustained (i.e., >6 months) increase in CD4 percentage to >15% in children aged <6 years, or an increase in CD4 count to >100 cells/mm$^3$ for children aged ≥6 years (as for adults). When the manifestation of CMV disease is ocular, such decisions should be made in close consultation with an ophthalmologist and consider factors such as magnitude and duration of CD4 count increase, anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.

All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy has been discontinued should continue to undergo regular ophthalmologic monitoring at 3- to 6-month intervals for early detection of CMV relapse and for immune reconstitution uveitis. CMV viral load or other markers of CMV infection (such as antigenemia or viral DNA tests) are not well standardized, and given that their role in predicting relapse remains to be defined, they are not recommended for routine monitoring of patients with any manifestation of CMV disease.[145,146]

### *Reinitiating Secondary Prophylaxis*

Relapse of CMV retinitis occurs in adults whose CD4 counts have decreased to <50 cells/mm$^3$ and whose anti-CMV maintenance therapies have been discontinued.[138,140] Reinstitution of secondary prophylaxis is recommended for adults with HIV when their CD4 counts fall to <100 cells/mm$^3$. For children with HIV in whom secondary prophylaxis has been discontinued because of immune reconstitution, secondary prophylaxis should be reinstituted in those aged <6 years when their CD4 percentages decrease to <15%, and in those aged ≥6 years when their CD4 cell counts decrease to <100 cells/mm$^3$.

## Recommendations

### *Primary Prevention*

**I. Is there an indication for CMV antibody testing in children with HIV who are asymptomatic (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 count <100 cells/mm$^3$ or CD4 percentage <10%) **(strong, low).**
- Children with perinatal HIV have a higher rate of CMV coinfection than children who are HIV exposed but uninfected. In children with HIV, CMV coinfection is associated with morbidity and mortality and, in the pre-ART era, HIV disease in children seemed to progress more quickly in those with CMV coinfection than in those without CMV infection. Although CD4 count is less predictive of risk of CMV disease in young children than in adults, children with HIV who have low CD4 counts are at increased risk of developing CMV disease.

**II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not undergoing 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 also is suggested for all HIV-exposed infants because their HIV status will be indeterminate during the 21-day period in which 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.
- The rate of congenital CMV infection among neonates born to mothers with HIV (2.2% to 6.5%) is higher than the prevalence of congenital CMV infection in the general population

(0.3% to 1.3%).[15,17,37,39-43] Co-transmission of congenital CMV may be higher among infants with HIV, with higher rates of congenital CMV infection reported among infants infected with HIV (4.3% to 21%) compared to HIV-exposed but uninfected infants (2.2% to 4.9%).[37,39,40,45-47] The rate of symptomatic congenital CMV infection also may be increased with HIV coinfection (23.1%) compared with those with CMV mono-infection (6.7%).[40] The rate of HIV progression in infants with congenital CMV/HIV dual infection is not well documented but may be faster than in infants with HIV mono-infection.[37,48] As the time of diagnosis for congenital CMV infection is limited to the first 21 days of life, a recommendation for CMV testing of HIV-exposed infants is influenced by the difficulty of diagnosing congenital CMV in infants beyond the first 21 days of age.

**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/mm$^3$ 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/mm$^3$ in children aged ≥6 years, or a 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/mm$^3$ for children ≥6 years of age, or >10% in children <6 years of age **(weak, low).**
- The rate of CMV end-organ disease in children with HIV remains low since the advent of ART.[54,81] Primary prophylaxis in adults with HIV is not recommended.[80] Data supporting the efficacy of antiviral prophylaxis against CMV in pediatric patients with HIV are lacking, but some experts would suggest using valganciclovir primary prophylaxis for children with severe immunosuppression to reduce the risk of CMV disease.

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

- Children with HIV aged <5 years who acquired CMV and are severely immunosuppressed (i.e., CD4 count <50 cells/mm$^3$ 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.
- The rate of CMV retinitis in children with HIV who are CMV seropositive has diminished substantially in the ART era. However, severe immunosuppression increases the risk of CMV retinitis. Therefore, children with HIV who are CMV seropositive and severely immunosuppressed should undergo routine ophthalmologic screening for CMV retinitis. CMV retinitis can also occur in patients without severe immunosuppression, so some experts recommend that young children with lesser degrees of immunosuppression undergo routine ophthalmologic screening until they are old enough to report visual symptoms reliably.

## *Treatment*

**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 and/or decreased mortality?**

- Treatment with antiviral therapy against CMV in addition to ART is recommended for CMV disease in children with HIV **(strong, moderate)**. 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)**. Combination treatment with IV ganciclovir and foscarnet may also be preferable as initial therapy to stabilize CMV neurologic disease and maximize response **(weak, very low).**
- In children with HIV and symptomatic congenital CMV infection, treatment with valganciclovir (or IV ganciclovir) for 6 months is recommended provided it can be started during the first month of life **(strong, moderate).** This is based on studies among children with symptomatic congenital CMV infection but without HIV.
- Treatment of CMV disease in children with HIV has not been studied rigorously, and recommendations are extrapolated from published results of studies in adults with HIV or in pediatric populations with non-HIV related immunosuppression (e.g., organ transplant recipients). Immune reconstitution via ART is necessary for long-term control of CMV disease. Most experts recommend CMV antiviral therapy to treat CMV disease until end-organ disease is controlled, and immune reconstitution is achieved. However, no pediatric studies have compared the rates of disease remission and mortality with anti-CMV therapy plus ART versus those with ART alone.
- A study of infants with symptomatic congenital CMV infection but without HIV who were treated with 6 months of oral valganciclovir demonstrated modest benefit in neurodevelopmental and hearing outcomes.[90] Similar studies have not been conducted in children with HIV.

## *Secondary Prevention*

**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 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 has also not been established.
- Courses of antiviral agents (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) do not cure CMV infection in any host. After induction therapy, secondary prophylaxis (chronic maintenance therapy) is given for most forms of CMV disease in the context of HIV until immune reconstitution is achieved, or in the absence of immune reconstitution, for the remainder of patients' lives. Recommendations for secondary prophylaxis in pediatric patients derive from adult studies given the lack of pediatric trials investigating secondary prophylaxis after CMV disease.

**VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children 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 (such as >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/mm$^3$ 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/mm$^3$ in those aged ≥6 years **(strong, moderate).**
- Studies regarding the safety and efficacy of discontinuing secondary prophylaxis for CMV disease in children with HIV have not been conducted. Studies in adults support the safety of discontinuing secondary prophylaxis for CMV retinitis in patients manifesting immune reconstitution with ART. Studies have not been performed in the setting of non-ocular CMV disease.

## Dosing Recommendations for Preventing and Treating Cytomegalovirus

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Prophylaxis | • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food<br>• For children aged 4 months to 16 years, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 x BSA x CrCl (up to maximum CrCl of 150 mL/min/1.73 $m^2$) orally once daily with food (maximum dose 900 mg/day) | N/A | Primary Prophylaxis Can Be Considered for—<br>• CMV antibody positivity and severe immunosuppression (i.e., CD4 count <50 cells/$mm^3$ in children age ≥6 years; CD4 percentage <5% in children age <6 years).<br>Criteria for Discontinuing Primary Prophylaxis<br>• Age ≥6 years with CD4 count >100 cells/$mm^3$<br>• Age <6 years with CD4 percentage >10%<br>Criteria for Considering Restarting Primary Prophylaxis<br>• Age ≥6 years with CD4 count <50 cells/$mm^3$<br>• Age <6 years with CD4 percentage <5% |
| Secondary Prophylaxis | • Ganciclovir 5 mg/kg body weight IV once daily, or<br>• For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food, or<br>• For children aged 4 months to 16 years, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 x BSA x CrCl (up to maximum CrCl of 150 mL/min/1.73 $m^2$) orally once daily with food, or<br>• Foscarnet 90–120 mg/kg body weight IV once daily | • Cidofovir 5 mg/kg body weight per dose IV every other week. Must be given with probenecid and IV hydration. | Secondary Prophylaxis Indicated for—<br>• Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse.<br>Criteria for Discontinuing Secondary Prophylaxis (All of the Following Criteria Must Be Fulfilled)<br>• Completed ≥6 months of ART<br>• Age <6 years with CD4 percentage ≥15% for >6 consecutive months<br>• Age ≥6 years with CD4 count >100 cells/$mm^3$ for >6 consecutive months<br>• Consultation with ophthalmologist (if retinitis)<br>o Routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis. |

## Dosing Recommendations for Preventing and Treating Cytomegalovirus

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| | | | Criteria for Restarting Secondary Prophylaxis<br>• Age <6 years with CD4 percentage <15%<br>• Age ≥6 years with CD4 count <100 cells/mm$^3$ |
| Treatment | Symptomatic Congenital Infection<br>• Ganciclovir 6 mg/kg body weight per dose IV every 12 hours for 6 weeks or valganciclovir 16 mg/kg body weight per dose orally twice daily for 6 months<br><br>Disseminated Disease and Retinitis<br>*Induction Therapy*<br>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours for 14–21 days (may be increased to 7.5 mg/kg body weight per dose IV twice daily)<br><br>*Chronic Maintenance Therapy*<br>• Ganciclovir 5 mg/kg body weight once daily for 5–7 days<br><br>Central Nervous System Disease<br>*Induction Therapy*<br>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours ***plus*** foscarnet 60 mg/kg body weight per dose IV every 8 hours (or 90 mg/kg body weight per dose IV every 12 hours) continued until symptomatic improvement | Disseminated Disease and Retinitis<br>*Induction Therapy*<br>• Foscarnet, 60 mg/kg body weight per dose IV every 8 hours or 90 mg/kg body weight per dose IV every 12 hours for 14–21 days<br><br>*Chronic Maintenance Therapy*<br>• Foscarnet 90–120 mg/kg body weight IV once daily<br><br>*Alternative Therapy for Retinitis (Followed by Chronic Maintenance Therapy; See Secondary Prophylaxis)*<br>• Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above).<br>  o Note: This is an option in older children who can receive the adult dose (based on their BSA) and in patients with mild disease.<br>• IV ganciclovir ***plus*** IV foscarnet (at above induction doses) may be considered as initial induction therapy in children with sight-threatening disease or for treatment following failure/relapse on monotherapy.<br>• Cidofovir is also used to treat CMV retinitis in adults who are intolerant to other therapies. Induction dosing in adults is 5 mg/kg body weight IV once weekly for 2 weeks, followed by chronic suppressive therapy | Data on valganciclovir dosing in young children for treatment of retinitis are unavailable, but consideration can be given to transitioning from IV ganciclovir to oral valganciclovir after improvement of retinitis is noted.<br><br>Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children.<br><br>Combination ganciclovir and foscarnet is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children is unknown, particularly if receiving optimized ART.<br><br>Chronic suppressive therapy (secondary prophylaxis) is recommended in adults and children following initial therapy of disseminated disease, retinitis, neurologic disease, or GI disease with relapse. |

## Dosing Recommendations for Preventing and Treating Cytomegalovirus

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| | *Chronic Maintenance Therapy*<br>• See Secondary Prophylaxis above. | (see above); however, data on dosing in children are unavailable. Must be given with probenecid and IV hydration. | |

Key: BSA = body surface area; ART = combined antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; CrCl = creatinine clearance; GI = gastrointestinal; IV = intravenous

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# Giardiasis (Last updated August 22, 2019; last reviewed August 22, 2019)

| Panel's Recommendations |
|---|
| I. **In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of giardiasis?** |
| • Giardiasis can be prevented by practicing good hygiene, not drinking or swimming in water that may be contaminated, and not eating food that may be contaminated (**expert opinion**). |
| • Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**). |
| • Initiating combination antiretroviral therapy (ART) in children with HIV infection to reverse or prevent severe immunodeficiency is the primary intervention to prevent severe enteric giardiasis (**strong, very low**). |
| II. **In children with HIV infection, what are the best interventions (compared with no intervention) to treat giardiasis?** |
| • Tinidazole and nitazoxanide are preferred therapies; metronidazole is the alternative recommended treatment for giardiasis in children (**strong, moderate**). |
| • Dehydration and electrolyte abnormalities should be corrected (**expert opinion**). |
| III. **In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of giardiasis?** |
| • Recurrent episodes of giardiasis can be prevented by practicing good hygiene and avoiding contaminated food and water (**expert opinion**). |
| • Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**). |
| Rating System |
| *Strength of Recommendation:* Strong; Weak |
| *Quality of Evidence:* High; Moderate; Low; or Very Low |

## Epidemiology

*Giardia duodenalis* (also known as *Giardia lamblia* or *Giardia intestinalis*) has a worldwide distribution, and giardiasis due to *G. duodenalis* is the most common nationally reportable intestinal parasitic disease identified by public health laboratories in the United States.[1] Giardiasis surveillance data show a bimodal age distribution, with the greatest number of reported cases occurring in children aged 1 to 9 years and adults aged 35 to 44 years. In the United States, most cases are reported between early summer and early fall and are associated with recreational water activities (e.g., swimming) and camping.[1]

Humans are the principal reservoir of *G. duodenalis*. The parasite is found in many animals species, although the role of zoonotic transmission is still being unraveled.[2-4] *G. duodenalis* is a flagellated protozoan with two forms: trophozoites and cysts. The infectious and environmentally resistant form is the cyst. After ingestion, each *Giardia* cyst produces two trophozoites in the proximal portion of the small intestine. Detached trophozoites pass through the intestinal tract, and form smooth, oval-shaped, thin-walled infectious cysts that are passed in feces. Duration of cyst excretion is usually self-limited but can vary and excretion may last for months. Studies in adults have shown that ingestion of as few as 10 to 100 fecally derived cysts is sufficient to initiate infection.[5] *Giardia* cysts are infectious immediately upon being excreted in feces and remain viable for at least 3 months in water at 4°C.[6] Although freezing will not eliminate the infectivity of *Giardia* cysts completely, heating, drying, or submersing them in seawater likely will.[6,7]

Infection with *Giardia* can occur directly by the fecal-oral route or indirectly via ingestion of contaminated water or food, but water contaminated with *Giardia* cysts appears to be the major reservoir and vehicle for spread of the parasite.[1,8] Most waterborne giardiasis outbreaks have been related to ingestion of untreated or improperly treated surface water.[9,10] Drinking untreated mountain stream water is a risk for hikers. Person-to-person spread of giardiasis occurs frequently in child care centers and in families of children with diarrhea.[11-13] Antigiardial host defenses are B-cell dependent, with secretory immunoglobulin A playing a major role in immunity. Individuals with humoral immunodeficiencies, such as X-linked agammaglobulinemia and hypogammaglobulinemia, who develop giardiasis are predisposed to chronic symptomatic disease.[14]

*G. duodenalis* infection is more common in certain high-risk groups, including children, employees and attendees of child care centers, patients and staff of institutions for people with developmental disabilities, men who have sex with men, people who ingest contaminated drinking water or recreational water (e.g., water from lakes, rivers, or inadequately treated swimming pools), travelers to disease-endemic areas of the world, close contacts of people with *Giardia*, people taking antibiotics,[13] and people exposed to *Giardia*-infected domestic and wild animals (e.g., dogs, cats, cattle, deer, and beavers).[12,13,15] There is little information on giardiasis in children with HIV infection, although *Giardia* has been associated with diarrhea in children with HIV infection and AIDS.[16,17] A recent study in Kenya described the association of enteric pathogens with HIV infection and HIV exposure in children. *Giardia* was the second most frequently associated pathogen, but the prevalence of *Giardia* was similar between the children with HIV and those exposed to HIV.[18]

Symptoms of giardiasis in individuals with HIV infection appear to be no more severe than in individuals who are HIV negative, and giardiasis is not typically considered a major cause of enteritis in patients with HIV.[19] There are no data in individuals with HIV but without advanced disease to suggest that the duration of parasite shedding or length of illness differs from that in individuals who are HIV negative. However, with progressive immunosuppression and reduced CD4 T-lymphocyte (CD4) cell counts, the risk of symptomatic *Giardia* infections increases. Studies in adults have demonstrated that enteritis due to *G. duodenalis* is a frequent event among patients with AIDS, especially in the most advanced stage of disease.[20] Research in adults with HIV infection from countries where giardiasis is endemic demonstrated that risk of *Giardia* infections and severity of disease increased with increasing immunosuppression and lower CD4 counts.[21,22] In a study of 75 adults with HIV infection in India, *G. duodenalis* was the most commonly isolated parasite, and patients with lower CD4 counts presented with significantly more enteric disease and chronic diarrhea.[23] In another study of 43 adults naive to combination antiretroviral therapy (ART), *G. duodenalis* was detected in one-third of patients and was significantly associated with lower CD4 counts (OR = 3.0 for CD4 counts ≤100 cells/mm$^3$).[24] A cohort study comparing giardiasis in adults with HIV infection in Brazil before and after the introduction of ART demonstrates that the incidence of enteric diseases caused by *Giardia* decreased after ART was introduced.[21] Given the evidence, it is reasonable to recommend initiation of ART and immune reconstitution as a primary mode of *Giardia* prevention, which is consistent with standard practice to treat all children with HIV infection in the United States with ART.

## Clinical Manifestations

The *Giardia* incubation period usually lasts 1 to 2 weeks and averages 7 days.[12] Symptomatic infection with *G. duodenalis* can cause a broad spectrum of clinical manifestations. Children usually present with short-lasting, acute watery diarrhea with or without low-grade fever, nausea, anorexia, and abdominal pain. In others, the infection has a more protracted intermittent course, characterized by foul-smelling stools associated with flatulence, abdominal distension, and anorexia. Malabsorption combined with anorexia can lead to significant weight loss, failure to thrive, and malnutrition in children.[25-27] Stools can initially be profuse and watery and later become greasy and foul smelling. Blood, mucus, and fecal leukocytes are absent. Varying degrees of malabsorption can occur, and abnormal stool patterns can alternate with periods of constipation and normal bowel movements. Post-*Giardia* infection lactose intolerance can occur in 20% to 40% of patients.[28] This syndrome may take several weeks to resolve and can contribute to malnutrition in children. Malnutrition and repeated episodes of *Giardia* infection in the first years of life have been associated with poor cognitive function in late childhood.[29,30] Additionally, a proportion of patients in whom *G. duodenalis* is diagnosed will also develop chronic GI symptoms such as post infections irritable bowel syndrome (PI-IBS).[30]

Asymptomatic *Giardia* infection is common.[31] Extraintestinal invasion can occur with trophozoites migrating into bile or pancreatic ducts. Extraintestinal manifestations were previously considered unusual, but recent evidence demonstrates that one third of patients will express long term extraintestinal symptoms, including ocular, muscular and metabolic complications.[30] Subsequent development of reactive arthritis has also been associated with giardiasis.[32,33]

## Diagnosis

Although diagnostic tests for *Giardia* infection have not been evaluated in children with HIV, the tests are expected to perform similarly as in other populations. A definitive diagnosis of *Giardia* infection is established by detection of *Giardia* trophozoites or cysts in stool specimens, duodenal fluid, or small-bowel tissue by microscopic examination using staining methods such as trichrome; direct fluorescent antibody (DFA) assays; detection of soluble stool antigens using enzyme immunoassays (EIA); or use of molecular techniques including polymerase chain reaction (PCR).[34-36] EIA or multiplex PCR testing is the currently recommended methodology based on assay performance.[36]

Identification of both trophozoites and cysts can be made on direct smears of concentrated specimens of stool. Appropriately conducted direct examination of stool establishes the diagnosis of *Giardia* in up to 70% of patients with a single examination and in 85% with a second examination. Identification of *Giardia* can be difficult because of intermittent excretion of cysts. Stool specimens should be examined within 1 hour after being passed. Trophozoites are more likely to be present in unformed stools because of rapid bowel transit time. Cysts, but not trophozoites, are stable outside the gastrointestinal (GI) tract.

When giardiasis is suspected, and stool specimens are negative, aspiration, biopsy, or both, of the duodenum or upper part of the jejunum should be performed. In a fresh specimen, trophozoites usually can be visualized on direct wet mount. Histologic evaluation of duodenal biopsy samples has low sensitivity for detecting infection, however, this diagnostic approach may be necessary in patients with clinical characteristics of *Giardia* infection but negative stool and duodenal fluid specimens. Cytology techniques such as brush cytology or examination of the formalin fixative from tissue samples enhance detection of *Giardia* over biopsy analysis alone.[37] The commercially available Entero-Test is an alternative method for obtaining duodenal fluid directly.[38]

Using polyclonal antisera or monoclonal antibodies against *Giardia*-specific antigens rather than direct microscopy has improved diagnostic testing for *Giardia*. Studies comparing EIA kits for detecting *Giardia* antigen in stool showed a sensitivity of 87% to 100% and a specificity of 100%. All fluorescent antibody tests had 100% sensitivity and specificity.[39] These rapid diagnostic tests can be positive before and after detection of organisms by microscopic examination. DFA and EIA were equally sensitive, and both were more sensitive than microscopy of permanently stained smears after concentration in formalin ethyl acetate.[40] Specific antibodies to *Giardia* have been detected and quantified by immunodiffusion, hemagglutination, immunofluorescence, and EIA, but a serologic test is not available commercially.

Commercially available multiplex PCR panels for the detection of GI pathogens, including *Giardia*, are now available. These tests are highly sensitive (92% to 100%) and specific (96.9% to 100%) and can detect multiple GI pathogens simultaneously.[41-43]

## Prevention Recommendations

### *Preventing Exposure*

Because *Giardia* organisms are most likely transferred from contaminated water or food, or by contact with an infected person or animal, avoidance of untreated water sources and hand washing with soap and water after exposure to potentially fecally contaminated material or contact with an infected person or animal are recommended. These recommendations are especially important in individuals with severe immunosuppression. A study in adults with HIV infection in the United States demonstrated the benefits of hand hygiene. In the intervention group, a regimen of intensive hand washing (hand washing after defecation, after cleaning infants who had defecated, before preparing food, before eating, and before and after sex) coupled with weekly reminder telephone calls regarding hand hygiene resulted in fewer *Giardia* infections.[44] Alcohol-based gels are ineffective against *Giardia* cysts and should not be used as a substitute for hand washing when exposure to *Giardia* is a concern.

In a hospital, standard precautions (i.e., use of gloves and hand washing after gloves are removed) should be sufficient to prevent transmission of *Giardia* from a patient with the infection to a susceptible person with HIV.

Before traveling to areas where the water may be contaminated or the safety of drinking water doubtful, travelers, hikers, and campers should be advised of methods to make water safe for drinking. These measures include using bottled water, disinfecting water by heating it to a rolling boil for 1 minute, or using a filter that has been tested and rated to National Safety Foundation Standard 53 or Standard 58 for cyst and oocyst reduction. Waterborne outbreaks of giardiasis can be prevented with a combination of adequate filtration of water sources, chlorination, and maintenance of water distribution systems.[1,9] Travelers should also be advised of the potential for transmission of giardiasis during use of contaminated recreational water (e.g., lakes, rivers, inadequately treated swimming pools).

### *Preventing First Episode of Disease*

No chemoprophylactic regimens are known to be effective in preventing giardiasis. However, because the risk of acquisition of giardiasis and the severity of infection increase with the severity of immunosuppression, ART to prevent or reverse severe immunodeficiency is a primary modality for giardiasis prevention in children with HIV. In the United States, it is standard practice to treat all children with HIV infection with ART.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

Effective ART and anti-parasitic therapy are the primary initial treatments for *Giardia* infections in children and adults with HIV infection.[21] Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Antimotility agents should be used with caution in young children. Patients with chronic diarrhea should be monitored for malabsorption leading to malnutrition.

The therapeutic efficacy of metronidazole against *Giardia* led to development of other nitroimidazole derivatives, such as tinidazole and secnidazole. These agents have the advantage of longer half-lives than metronidazole, making them suitable for single-daily-dose therapies. A single, 2-g dose (or the equivalent pediatric dosing of 50 mg/kg in a single dose) of tinidazole has demonstrated cure rates ranging from 80% to 100% and is also associated with improved medication adherence. Cure rates of patients with *Giardia* have been shown to be consistently higher with the use of tinidazole than with use of other anti-parasitic drugs such as metronidazole, nitazoxanide, mebendazole, albendazole and chloroquine.[45-47] Tinidazole is approved for use in children 3 years and older.The drug is available in tablets, which can be crushed in flavored syrup for patients unable to swallow tablets.

Nitazoxanide is approved in the United States for treatment of infections due to *G. duodenalis* in patients 1 year or older. A randomized, controlled clinical trial in adolescents and adults without HIV infection in Egypt demonstrated nitazoxanide's efficacy against placebo.[48] Nitazoxanide has been compared with metronidazole and mebendazole to treat giardiasis in children and was found to be equally effective, with eradication rates for *G. duodenalis* of 71% to 81% with nitazoxanide treatment.[49]

Metronidazole was determined to be therapeutic against giardiasis in 1962. Since then, clinicians have used metronidazole and other nitroimidazoles as the mainstay of therapy of giardiasis. Metronidazole is the drug most often used for giardiasis treatment worldwide. Children have been included in many of the clinical trials of metronidazole, with outcomes similar to those in adults (median efficacy, 94%) with 5- day to 10-day regimens.[50] Metronidazole is not available in a standard liquid form, but a suspension can be prepared by thoroughly crushing metronidazole tablets, using glycerin as a lubricant, and suspending the mixture in flavored syrup.[51] Despite widespread and accepted use of metronidazole against *Giardia,* it has not been approved by the U.S. Food and Drug Administration for this indication.

Quinacrine has been used in combination therapy for cases in which treatment failure was suspected.[52] The severity of side effects prevented clinicians from using quinacrine as an initial therapeutic choice or first-line alternative, particularly in children. A bitter taste and vomiting led to the drug's lower efficacy in children, probably because of poor medication adherence.[53] Quinacrine is no longer available in the United States and has been discontinued by the manufacturer.[54,55]

## *Monitoring and Adverse Events (Including IRIS)*

Patients with chronic diarrhea should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In severely ill patients, total parenteral nutrition may be indicated.

Adverse effects reported with tinidazole are not as common as with metronidazole but do include bitter taste, vertigo, and GI upset.[50]

Nitazoxanide is generally well tolerated with no significant adverse events noted in human trials. Adverse events have been mild and transient and principally related to the GI tract, such as abdominal pain, diarrhea, and nausea. Nitazoxanide has been well tolerated up to the maximum dose of 4 g when taken with or without food, but the frequency of GI side effects increases significantly with the dose level.[49]

The most common side effects of metronidazole treatment include headache, vertigo, nausea, and a metallic taste. Nausea occurs in 5% to 15% of patients given standard multiday courses. In addition, pancreatitis, central nervous system toxicity at high doses, and transient, reversible neutropenia have been attributed to metronidazole.[50]

Among patients taking quinacrine, 4% to 5% had yellow/orange discoloration of the skin, sclerae, and urine beginning about 1 week after starting treatment, and continuing up to 4 months after the drug was discontinued. Other common side effects of quinacrine included nausea, vomiting, headache, and dizziness. Quinacrine can precipitate hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals.[53]

Immune reconstitution inflammatory syndrome has not been associated with giardiasis or its treatment.

## *Managing Treatment Failure*

The most important steps for management of giardiasis treatment failure are supportive treatment, optimal use of ART to achieve full virologic suppression, and modification of antiparasitic therapy. Treatment failures have been reported with all of the common anti-*Giardia* agents. It is important that clinicians differentiate between resistance to treatment and reinfection, which is common in *Giardia* endemic regions and situations where poor hygiene facilitates fecal-oral transmission. Resistance to most anti-*Giardia* agents has been documented, but there is no consistent correlation between *in vitro* resistance and clinical failure.[50] Clinically resistant strains have been treated with longer repeated courses or higher doses of the original agent or a drug from a different class to avoid potential cross-resistance. Using combination regimens that include metronidazole-albendazole, metronidazole-quinacrine, or other active drugs or giving a nitroimidazole plus quinacrine for at least 2 weeks have both proven successful against refractory infection. Combination therapy with albendazole-praziquantel, nitazoxanide–albendazole, and bacitracin –neomycin has been investigated in clinical trials. However, randomized controlled trials of combination therapy are limited and the optimal combinations need to be clarified, particularly in cases of treatment failure associated with suspected drug tolerance.[56] In patients with AIDS who have severe giardiasis, prolonged or combination therapy may be necessary.[52,57]

## *Preventing Recurrence*

No known pharmacologic interventions effectively prevent recurrence of giardiasis. Reinfection is frequent in endemic areas, or in situations where hygiene is poor or contaminated water (e.g., in private wells) is not adequately treated. Reinfection can be prevented by consistently practicing good hand hygiene, but particularly after defecation and handling of soiled diapers. Hand hygiene should also be practiced before preparing and eating food.[12] To reduce risk of disease transmission, children with diarrhea should be excluded from child care settings until the diarrhea has stopped. Children with giardiasis should not frequent recreational water venues for 2 weeks after symptoms resolve. Additional information about recreational water illnesses and how to stop them from spreading is available at https://www.cdc.gov/healthywater/swimming/ and at https://www.cdc.gov/parasites/giardia/prevention-control.html.

### *Discontinuing Secondary Prophylaxis*

Not applicable.

## Recommendations

**I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of giardiasis?**

- Giardiasis can be prevented by practicing good hygiene, not drinking or swimming in water that may be contaminated, and not eating food that may be contaminated (**expert opinion**).

  Because giardiasis results from ingestion of infectious cysts that are passed in the feces of infected individuals that may contaminate food or water, careful hand washing and washing of fruits and vegetables are recommended.

- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).

  A randomized trial of an intensive hand washing intervention (i.e., handwashing after defecation, after cleaning infants who had defecated, before preparing food, before eating, and before and after sex) in 148 adults with HIV infection in the United States resulted in fewer episodes of diarrheal illness and *Giardia* infections during a one year period, demonstrating the effectiveness of hand washing.[44]

- Combination antiretroviral therapy of children with HIV infection to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric giardiasis (**strong, very low**).

  A case-control study comparing giardiasis in adults with HIV infection in Brazil before and after the introduction of ART demonstrated that the incidence of enteric diseases caused by *Giardia* decreased after the introduction of ART.[21] Given the evidence, it is reasonable to recommend initiation of ART and immune reconstitution as a primary mode of giardiasis prevention.

**II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat giardiasis?**

- Tinidazole and nitazoxanide are preferred, and metronidazole is the alternative recommended treatment for giardiasis in children (**strong, moderate**).

  Clinical trials in children without HIV infection have demonstrated the efficacy of single dose tinidazole in comparison to other anti-parasitic drugs such as nitazoxanide, mebendazole, albendazole and chloroquine.[45-47] Tinidazole can be used in children 3 years and older. Nitazoxanide can be used in children 1 year or older. Metronidazole is inexpensive and widely available and has been used by clinicians as the mainstay of therapy of giardiasis. Metronidazole has been shown to be less efficacious than tinidazole, but comparable to nitazoxanide.[7,45,58]

- Dehydration and electrolyte abnormalities should be corrected (**expert opinion**).

  There are no studies that address this specific management issue in giardiasis. However, recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.

**III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of giardiasis?**

- Recurrent episodes of giardiasis can be prevented by practicing good hygiene and avoiding contaminated food and water (**expert opinion**).
- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).

Good hygiene, including frequent hand washing and avoiding contaminated food and water, are recommended to prevent both initial and recurrent *Giardia* infections.

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## Dosing Recommendations for Prevention and Treatment of Giardiasis

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Prophylaxis | ART to avoid advanced immunodeficiency | N/A | N/A |
| Secondary Prophylaxis | N/A | N/A | N/A |
| Treatment | Tinidazole 50 mg/kg orally, administered as one dose given with food (maximum dosage tinidazole 2 g). **Note:** Based on data from children who are HIV-negative.<br><br><u>Nitazoxanide</u>:<br>• Aged 1–3 Years: Nitazoxanide 100 mg by mouth every 12 hours with food for 3 days<br>• Aged 4–11 Years: Nitazoxanide 200 mg by mouth every 12 hours with food for 3 days<br>• Aged ≥12 Years: Nitazoxanide 500 mg by mouth every 12 hours with food for 3 days<br>• **Note:** Based on data from children who are HIV-negative | Metronidazole 5 mg/kg by mouth every 8 hours for 5–7 days. **Note:** Based on data from children who are HIV-negative. | Tinidazole is FDA-approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed.<br><br>Metronidazole has a high frequency of GI side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA-approved for the treatment of giardiasis.<br><br><u>Supportive Care</u>:<br>• Hydration<br>• Correction of electrolyte abnormalities<br>• Nutritional support<br><br>Antimotility agents (e.g., loperamide) should be used with caution in young children. |

**Key:** ART = antiretroviral therapy; FDA = U.S. Food and Drug Administration; GI = gastrointestinal

# 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 coinfected 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-coinfected 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-coinfected children who require treatment of both infections, a cART regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**.
- For HIV/HBV-coinfected 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-coinfected 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*

***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*

## Epidemiology

Chronic hepatitis B virus (HBV) infection is defined as persistence of serum hepatitis B surface antigen (HBsAg) for >6 months. The risk of developing chronic HBV infection after acute infection correlates inversely with age and immune competence at HBV infection. In HBV-infected patients, chronic HBV infection develops in about 90% of infants, 25% to 50% of children aged 1 to 5 years, and 6% to 10% of older children and adolescents; individuals with immunocompromising conditions (e.g., renal failure) are also at increased risk of developing chronic HBV infection.[1-4]

Infant and childhood HBV infection can be acquired perinatally, parenterally, or postnatally through household contact. It can also be acquired parentally or through sexual transmission. HIV/HBV-coinfected pregnant women can transmit HIV, HBV, or both to their infants; it is not known if maternal HIV coinfection modifies the risk of HBV perinatal transmission. Horizontal transmission of HBV can occur through interpersonal contact with non-intact skin or mucous membranes with blood or body fluids that contain HBV (e.g., injuries, wounds) or from sharing household objects (e.g., toothbrushes, razors). Universal hepatitis B vaccination of newborns has dramatically lowered chronic HBV infection in children and reduced the rates of HBV-related morbidity and mortality in the United States. The risk from blood transfusions in countries with blood bank screening is estimated to be very low (1.37 per million donations).[5] Maternal HBV infection is not a contraindication to breastfeeding.

Adolescents are at risk of HBV infection through sexual activity or injection-drug use. In a study of HIV-infected adolescents infected through sexual activity or injection-drug use at 43 Pediatric AIDS Clinical Trial Group centers, 19% had evidence of current or resolved HBV infection; the rate of current or resolved HBV infection in HIV-infected adolescent girls was twice the U.S. population-based rates for HIV-uninfected adolescent girls and, for adolescent boys, nearly seven times higher.[6] Substance abuse and sexual activity increase the risk of HIV/HBV coinfection in adolescents, particularly in men who have sex with men (MSM).[7]

Most children who acquire HBV perinatally are initially immunotolerant to HBV and may remain immunotolerant for a decade or more. Although these children have high HBV DNA levels, serum transaminase levels are usually normal, and necroinflammatory liver disease is minimal. Childhood-acquired HBV infection, in contrast, is characterized by lower HBV DNA levels, greater serum transaminase elevation, and higher necroinflammatory liver disease than in perinatally acquired HBV infection.[8]

Data from the National Health and Nutrition Examination Survey, 1999–2004, indicate that 0.51% (95% CI: 0.3%–0.9%) of children aged 6 to 19 years had ever been infected with HBV.[9] Only 1 small case series exists on the prevalence of chronic HBV infection in HIV-infected children at an inner city hospital in the United States, finding 2.6% prevalence in 228 HIV-infected children.[10]

## Clinical Manifestations

Most acute HBV infections in children are asymptomatic.[11] Prodromal symptoms of lethargy, malaise, fatigue, nausea, and anorexia can occur. Jaundice and right-upper-quadrant pain can follow and, less commonly, hepatomegaly and splenomegaly. Gianotti-Crosti syndrome (papular acrodermatitis), urticaria, macular rash, or purpuric lesions may be seen in acute HBV infection. Extrahepatic manifestations associated with circulating immune complexes that have been reported in HBV-infected children include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. However, rare cases of acute hepatic failure have occurred during perinatal and childhood HBV infection.[12,13]

Most children with chronic HBV infection are asymptomatic. One quarter of infants and children with chronic HBV eventually will develop cirrhosis or hepatocellular carcinoma (HCC).[14,15] However, these sequelae usually develop over 2 to 3 decades and rarely occur during childhood.[16,17] Development of HCC correlates with HBV DNA levels and duration of HBV infection, with the highest risk in people infected in early life.[18] HIV/HBV-coinfected adults are at increased risk of cirrhosis, end-stage liver disease, and liver-related mortality.[19]

## Diagnosis

Testing for HBV infection should be performed in any child whose mother is known to be infected with HBV as well as children from groups at high risk of HBV infection, including those who are HIV-infected and who are foreign-born in regions of high and intermediate HBV endemicity (HBsAg-positive prevalence ≥2%). Adolescents and young adults with HIV infection, histories of injection-drug use, high-risk sexual contact, or MSM, should also undergo testing for HBV infection. Based on high prevalence of HBV infection in HIV-infected children and adolescents, HIV-infected children and adolescents and HIV-uninfected infants born to HBsAg-positive women should be tested for HBsAg as soon as possible after HIV diagnosis **(AII)**.[6,7,20]

HBsAg is the first marker detectable in serum, appearing 30 days after infection; it precedes the elevation of serum aminotransferase levels and the onset of symptoms. Necroinflammatory liver disease then can occur, during which serum transaminase levels increase, along with high HBV DNA levels and HBeAg positivity. HBeAg correlates with viral replication, DNA polymerase activity, infectivity, and increased severity of liver disease. Antibody to hepatitis B core antigen (anti-hepatitis B core antigen [HBc] immunoglobulin M [IgM]) appears 2 weeks after HBsAg and the anti-HBc immunoglobulin G (IgG) persists for life, but should not be confused with passively transferred maternal anti-HBc IgG that can be detectable in the infant up to ages 12 to 18 months or later. In self-limited infections, HBsAg is usually eliminated in 1 to 2 months, and hepatitis B surface antibody (anti-HBs) develops during convalescence. Anti-HBs indicates immunity from HBV infection. Despite immunity, HBV is incorporated into the human genome, where it can reactivate years later if a person becomes immunocompromised.[21] After recovery from natural infection, both anti-HBs and anti-HBc usually are present. In patients who become chronically infected (i.e., persistently positive for HBsAg beyond 6 months), anti-HBs is undetectable. Patients who have been vaccinated may have detectable anti-HBs but not anti-HBc or HBsAg. Patients who may have been inadvertently vaccinated after recovery from HBV infection should have detectable anti-HBs and anti-HBc upon post-vaccination testing (see Table 1, located at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm#tab1, for review of interpretation of serologic test results for HBV infection).

HBeAg seroconversion, defined as loss of HBeAg, followed by the production of antibodies to HBeAg (e.g., anti-HBe), usually heralds transition of the HBV-infected person to the inactive carrier state (HBsAg remains positive); however, some patients may develop HBeAg-negative chronic hepatitis. Variable rates of HBeAg seroconversion have been reported in children infected perinatally with HBV ranging from 10% to 75% in the first 2 to 4 decades but it is very infrequent in children aged <3 years.[22,23] In contrast, higher rates of HBeAg seroconversion occur in childhood-acquired HBV infection, with 70% to 80% of children acquiring anti-HBe by the second decade of life.[16] HBeAg seroconversion usually is followed by reduction in serum HBV DNA levels, an initial increase and then subsequent normalization of serum transaminase levels, followed by resolution of necroinflammatory liver disease.[16] Development of cirrhosis and HCC is more common in patients with delayed HBeAg seroconversion.[24] HBeAg-negative infection (pre-core mutant) is uncommon in children.[3]

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

## Prevention Recommendations

### *Preventing Exposure*

All pregnant women should be tested for HBsAg during the first prenatal visit **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk of HBV infection (e.g., injection-drug users, women with intercurrent sexually transmitted diseases, women with multiple sex partners) **(BIII)**.

Pregnancy is not a contraindication or precaution to hepatitis B vaccination for women who have not previously been vaccinated; current hepatitis B vaccines contain noninfectious HBsAg and should cause no risk to the fetus. Pregnant women who are identified as being at risk of HBV infection during pregnancy should be vaccinated.[25]

### *Preventing Disease*

All infants born to HBV-infected women, including HIV co-infected women, should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) 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, but not before age 24 weeks **(AI)** (Figures 1 and 2).[26] For preterm infants weighing <2000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches 1 month of age **(AI)**.[26] In addition, term and preterm (birth weight <2000 g) infants born to women whose HBsAg status is unknown at delivery should receive the first dose of hepatitis B vaccine within 12 hours of birth. Infants weighing <2000 g should also receive HBIG within 12 hours of birth. Women with unknown HBsAg status should be tested as soon as possible. HBIG should be administered to term infants born to women whose HBsAg-test is found to be positive, or within 7 days of life when a mother's test results remain unknown.[26]

A 3-dose hepatitis B vaccine regimen is 70% to 95% effective in preventing HBV infection in HBV-exposed infants and combined with HBIG, is 85% to 95% effective. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9 to 18 months in infants born to HBsAg-positive women **(BIII)**. The level of anti-HBs that is considered protective is ≥10 mIU/mL. Infants who are HBsAg-negative and have anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series of hepatitis B vaccine and retested 1 to 2 months after the final vaccine dose **(BIII)**.[26]

The 3-dose series of hepatitis B vaccine also is recommended for *all* children and adolescents aged <19 years who were not previously vaccinated. However, antibody responses to hepatitis B vaccination may be diminished in HIV-infected children, especially in older children or those with CD4 T lymphocyte (CD4 cell) counts <200 cells/mm$^3$.[27,28]

For this reason, HIV-infected infants, children, and adolescents should be tested for quantitative anti-HBs 1 to 2 months after completing the vaccination series and, if anti-HBs levels are <10 mIU/mL, revaccinated with a second 3-dose series of hepatitis B vaccine **(AIII)**.

Limited data suggest modified hepatitis B vaccine dosing regimens, including a doubling of the standard antigen dose and use of combined hepatitis A and B (HAV/HBV) vaccine, can increase response rates in HIV-uninfected non-responders[29] and in HIV-infected adults and adolescents.[30-32] Therefore, use of double-dose HBV vaccine or combination HAV/HBV vaccine may be considered for HBV vaccination in HIV-infected adolescents **(BI)**.

Waning of HBsAb levels below 10 mIU/mL after HBV re-immunization in HIV-infected children is common, but the need for booster doses of hepatitis B vaccine in HIV-infected individuals has not been determined.[33] The American Academy of Pediatrics Committee on Infectious Disease recommends annual anti-HBs testing and booster doses when the anti-HBs levels decline to <10 mIU/mL for hemodialysis patients and other immunocompromised people at continued risk of hepatitis B infection **(CIII)**.[34] HBV-infected children should be advised not to share toothbrushes or other personal-care articles that might be contaminated with blood (e.g., razors, tweezers, nail clippers) and to cover open or draining wounds. Although efficiency of sexual transmission of HBV is relatively low, safe-sex practices should be encouraged for all sexually active HIV-infected adolescents and young adults; barrier precautions (e.g., latex condoms) are recommended to reduce the risk of exposure to sexually transmitted pathogens, including HBV.

## Treatment Recommendations

### *Treating Disease*

#### General Issues

All children should receive HAV vaccination at age 12 to 23 months with the 2 doses in the series administered at least 6 months apart.[35] Children who are not fully vaccinated by age 2 years can be vaccinated at subsequent visits. The hepatitis A vaccine is also recommended for children aged ≥24 months who were not previously vaccinated and who have chronic liver disease (including chronic HBV infection) and other chronic diseases (Figures 1 and 2).

Treatment of pediatric HBV infection should be based on multiple factors, including a child's age, age at acquisition of infection, HBV DNA levels, and serum transaminase levels. Antiviral therapy regimens for chronic HBV are approved only for children aged >2 years who have compensated liver disease.

HIV-infected children who are not receiving anti-HBV therapy should be closely monitored with determination of serum aminotransferase levels every 6 months. If serum transaminase levels are persistently elevated (more than twofold the upper limit of normal for ≥6 months), HBeAg, anti-HBe, and HBV DNA levels should be obtained before the initiation of anti-HBV therapy. Assessment of serum transaminases and HBV DNA levels over time can identify patients who may be in the process of spontaneous HBeAg seroconversion and who would thus not require treatment. Liver biopsy is not required before treatment but may help to determine the severity of hepatic inflammation and fibrosis and to exclude other causes of liver disease.[36,37]

No clear recommendations exist for treating chronic childhood HBV infection. HBV-infected children often have milder disease than adults and may show spontaneous HBeAg seroconversion. Few large randomized controlled trials exist of antiviral therapies for chronic HBV infection in childhood. Moreover, the long-term safety of many of the agents used to treat chronic HBV infection in adults is unknown in children. However, pediatric liver experts at a 2010 consensus meeting recommended that anti-HBV treatment be considered in children aged >2 years with chronic HBV infection and a duration of necroinflammatory liver disease >6 months.[36]

Indications for treatment of chronic HBV infection in HIV-coinfected children are the same as in HBV-infected, HIV-uninfected children:

- Evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>10,000–100,000 IU/mL), irrespective of HBeAg positivity, 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)**.[3,38]

Children without necroinflammatory liver disease do not warrant anti-HBV therapy **(BIII)**. Anti-HBV 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)**.

The goals of treatment for children with chronic HBV infection are identical to those for adults: suppression of HBV replication, normalization of serum transaminase levels, acceleration of HBeAg seroconversion (in those who are HBeAg positive), preservation of liver architecture, and prevention of long-term sequelae, such as cirrhosis and HCC.

Treatment of chronic HBV infection is evolving; consultation with providers with expertise in treating chronic HBV infection in children is recommended.

### *Treating Chronic Hepatitis B Infection in Adults and Adolescents*

Seven medications have been approved to treat chronic HBV infection in adults: interferons (both standard and pegylated), nucleoside analogues (i.e., lamivudine, telbivudine, and entecavir), and the nucleotide analogues, adefovir and tenofovir disoproxil fumarate (tenofovir). The FDA-approved HIV antiretroviral (ARV) medication emtricitabine also has significant activity against HBV, although it is not approved for this indication. Preferred initial therapies for adults who have chronic HBV without HIV infection include pegylated interferon-alfa (PEG-IFN-α), entecavir, or adefovir monotherapy. In HIV-infected adults who have chronic HBV infection, treatment for hepatitis B should be considered for those who are HBeAg-positive with HBV DNA ≥20,000 IU/mL (>$10^5$ copies/mL), HBeAg-negative with HBV DNA ≥2000 IU/mL (>$10^4$ copies/mL), patients who have persistent serum transaminase elevation, and those with evidence of cirrhosis or fibrosis.[19] Treatment of HBV infection is now recommended for all adults with concomitant HIV infection (*Adult Opportunistic Infection* and *Antiretroviral Guidelines*). This has not been recommended for children, however, and given the lack of data on this issue, a similar recommendation cannot be made at this point.

Treatment options for HBV in HIV-infected patients must account for the goals of therapy and the impact treatment may have on both HIV and HBV replication. In coinfected patients who require treatment for chronic HBV, HIV, or both, many experts would initiate a fully suppressive combined antiretroviral therapy (cART) regimen that includes two drugs active against HBV (tenofovir and either lamivudine or emtricitabine). This approach may reduce the risk of immune reconstitution inflammatory syndrome (IRIS), particularly in patients with advanced immunodeficiency. The combination of tenofovir with lamivudine was demonstrated to be more effective in suppressing HBV in coinfected adults than either drug alone and prevents development of lamivudine resistance.[39] In instances in which HIV treatment cannot be given but treatment of HBV infection is needed, PEG-IFN-α can be used alone because it does not lead to development of drug-resistant HIV or HBV mutants. Anti-HBV drugs with anti-HIV activity should not be given in the absence of a fully suppressive ARV regimen, because anti-HBV drugs such as tenofovir, entecavir, emtricitabine, lamivudine, and likely telbivudine given without additional ARV drugs in an HIV-suppressive regimen likely would produce resistant HIV in the recipient (see *Guidelines for Prevention and Treatment of Opportunistic Infection in Adolescents and Adults with HIV Infection*).

### *Treating Chronic Hepatitis B Infection in HIV-Uninfected Children*

Only two drugs (IFN-α [standard] monotherapy or lamivudine monotherapy) are FDA-approved to treat chronic HBV in young children (1-11 years old) **(AI)**.[40,41] Four other drugs are approved for treatment of chronic HBV in older children: adefovir and tenofovir (children aged ≥12 years) and entecavir and telbivudine (children aged ≥16 years) **(AI)**.[42-45] While tenofovir is approved for treatment of HIV infection in children aged ≥2 years, it is not approved for treatment of HBV in children under 12 years old.

The limited pediatric trials of these agents show that although they are well-tolerated by children, response rates are similar to adults (~25% HBeAg seroconversion), and treatment generally does not eliminate HBV infection.[46,47] There is some evidence for enhanced loss of HBsAg in children treated with IFN in comparison to those treated with lamivudine.[40,48] In HIV-uninfected children, HBeAg seroconversion rates after 1 year of treatment are similar.[3] IFN-α treatment is administered for only 6 months but requires subcutaneous administration and has more frequent side effects, including growth impairment. Although lamivudine is administered orally and has a lower rate of side effects, it requires a longer duration of therapy and has a high rate of resistance if taken for an extended time.[3]

Although various combination regimens involving sequential or concurrent lamivudine and standard or PEG-IFN-α have been studied in children or adults with chronic HBV, superior treatment response with combination therapy over monotherapy with standard or PEG-IFN-α or lamivudine has not been demonstrated; however, lamivudine resistance rates may be lower with combination therapy.[49-58] A recent study of children with immunotolerant HBV infection suggested possible benefit from sequential lamivudine and IFN-α therapy, with 78% of patients clearing HBV DNA by the end of treatment.[57]

However, IFN-α (standard or pegylated) therapy in combination with oral antiviral therapy cannot be recommended for HBV infection in HIV-uninfected children until more data are available **(BII)**.

### *Treating HBV/HIV-Coinfected Children*

None of the clinical studies of treatment of chronic HBV infection have specifically studied children with HIV/HBV coinfection. Choice of antiviral therapy for the HIV/HBV coinfected child involves consideration of whether HBV treatment, HIV treatment or treatment for both infections is warranted. Further study is needed to inform recommendations for antiviral therapy of children and adolecents with HIV/HBV coinfection.

If treatment of chronic HBV but not HIV infection is indicated, standard IFN-α is the preferred agent **(BIII)**. Adefovir also can be considered in children aged 12 years or older **(BIII)**. Antiviral drugs with activity against HIV (e.g., lamivudine, emtricitabine, tenofovir, entecavir, and likely telbivudine) should be avoided in the absence of a fully suppressive cART regimen to prevent development of drug-resistant HIV mutations. Despite *in vitro* evidence of anti-HIV activity of adefovir, there is no clinical evidence that adefovir monotherapy induces HIV drug resistance.[59]

If treatment of HIV infection but not chronic HBV is indicated, avoiding use of a cART regimen that contains only one ARV drug with activity against HBV (e.g., lamivudine, emtricitabine, or tenofovir) can prevent development of HBV drug resistance. Thus, in coinfected children who can receive tenofovir, use of a cART regimen that contains two drugs effective against HBV (tenofovir plus lamivudine or emtricitabine) can be considered **(BIII)**. However, for coinfected children aged < 2 years who need HIV but not HBV treatment, many experts would use a standard cART regimen that includes lamivudine (or emtricitabine). The optimal treatment approach needs further study.

If treatment for both HIV and chronic HBV is indicated and the child is lamivudine-naive, a cART regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**. A regimen containing tenofovir and lamivudine (or emtricitabine) should be considered for use in HIV-infected children aged ≥2 years, based on extrapolation from evidence in adults with HIV/HBV coinfection and adolescents with HBV monoinfection[42] but limited by absence of data evaluating use of tenofovir for treatment of HBV infection in HBV-monoinfected or HIV/HBV-coinfected children or HIV/HBV-coinfected adolescents **(BIII)**.

If treatment for HIV and chronic HBV is indicated, a child is already receiving HIV-suppressive cART including lamivudine (or emtricitabine), and plasma HBV DNA is detectable, HBV lamivudine resistance can be assumed. However, because HBV drug-resistant isolates may have lower replicative capacity, some experts recommend no change in therapy, although this recommendation is controversial **(CIII)**. Treatment options for such children who require HBV therapy include adding standard IFN-α **(BIII)**, or adefovir in children who can receive adult dosing **(BIII)**, or use of tenofovir (with continued lamivudine or emtricitabine) in the cART regimen in children aged ≥2 years **(BIII)**.

Data are insufficient on other anti-HBV drugs in children to make recommendations.

#### Interferons

Standard IFN-α-2a or -2b has received the most study in children who have chronic HBV infection (without HIV infection) and is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged ≥2 years who warrant treatment **(AI)**.

In a review of 6 randomized clinical trials in 240 HBV-infected children aged >1.5 years, IFN-α therapy resulted in HBV DNA clearance in 35% of treated children, HBeAg clearance in 10%, and normalization of serum transaminase levels in 39% at treatment completion.[60] Six to 18 months after therapy discontinuation, 29% of children had persistent clearance of HBV DNA, and 23% demonstrated HBeAg clearance. Children most likely to respond to IFN treatment are younger and have higher baseline serum transaminase levels and lower baseline HBV DNA levels.[46,61-63] Response is less likely (10%) in those with normal serum transaminase levels, high HBV DNA levels, HBV genotypes C or D, or HBeAg-negative chronic HBV infection.

IFN-α therapy is the preferred agent to treat chronic hepatitis B in HIV-coinfected children who do not require cART for their HIV infection **(BIII)**.

The standard course of IFN-α therapy for HIV-uninfected children is 24 weeks. PEG-IFN-α, which results in more sustained plasma interferon concentrations and can be administered by injection once weekly for 48 weeks, has proven superior to standard IFN-α in treating HBV-infected adults.[50,64] However, the limited data on use of pegylated IFN-α in children come from treatment of hepatitis C infection, and appropriate dosing information is not available for use of pegylated IFN-α to treat chronic HBV infection in children.[65-67]

### Lamivudine

Lamivudine (3TC) is an oral nucleoside analogue that inhibits HBV replication. It is approved for use in children aged 2 to 17 years who have compensated liver disease from chronic HBV infection. In a placebo-controlled trial in HIV-uninfected children with chronic HBV infection, lamivudine was well tolerated, with virologic response (clearance of HBV DNA and HBeAg) in 23% of children receiving 52 weeks of lamivudine therapy, compared with 13% in placebo recipients.[41] Response rates were higher (35%) for children with baseline serum transaminases more than two times normal.[41] In a 2-year, open-label extension of this study, 213 children who remained HBeAg-positive after 1 year of therapy were continued on lamivudine treatment; virologic response was seen in 21% of the original lamivudine recipients, compared with 30% of prior placebo recipients, indicating that additional clinical response could occur over time with prolonged treatment.[68] However, longer duration of lamivudine therapy also was associated with progressive development of lamivudine-resistant HBV, with base pair substitutions at the tyrosine-methionine-aspartate-aspartate (YMDD) locus of HBV DNA polymerase.

Lamivudine should not be used as a single agent for treatment of chronic HBV infection in HIV-infected children who are not receiving cART because of the risk of HIV resistance to lamivudine **(CIII)**; as discussed above, lamivudine should be used only in HIV/HBV-coinfected children in combination with other ARV drugs in a cART regimen **(BIII)**. The dose of lamivudine required to treat HIV infection is higher than that for treating pediatric chronic HBV infection alone; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfected children to avoid development of lamivudine-resistant HIV **(AIII)**.

Lamivudine resistance should be suspected if HBV DNA levels increase by 1 to 2 log during antiviral therapy. Such increases may precede increases in serum transaminase levels (hepatic flare) and liver decompensation.[63]

### Emtricitabine

Emtricitabine is structurally similar to lamivudine and is active against HBV and HIV, although not approved for treatment of chronic HBV infection. Like lamivudine, emtricitabine also is associated with relatively rapid onset of HBV and HIV drug resistance, and patients with suspected lamivudine resistance should be assumed to have cross-resistance to emtricitabine.

Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic HBV infection and not additive **(AIII)**. As with lamivudine, emtricitabine should not be used to treat chronic HBV infection in coinfected children who are not being treated with cART for their HIV infection because of the risk of HIV-associated resistance mutations **(CIII)**.

### Adefovir

Adefovir dipivoxil is an oral nucleotide analogue active against HBV. Although active against HBV, adefovir has minimal anti-HIV activity, and HIV resistance has not been observed in patients receiving a 10-mg daily dose of adefovir for 48 weeks.[59] HBV resistance is much lower to adefovir than to lamivudine, reportedly 2% after 2 years, 4% after 3 years, and 18% after 4 years of therapy in adults.[69] These adefovir-associated mutations in HBV *Pol* gene result in only a modest (threefold to eightfold) increase in the 50% inhibitory concentration and are partially cross-resistant with tenofovir. Adefovir is now FDA-approved for adults who require treatment for chronic HBV infection but do not yet require treatment for HIV. Adefovir has been studied in HIV/HBV-coinfected adults with lamivudine-resistant HBV infection, and HBV suppression was demonstrated.[59] Safety and effectiveness of adefovir for treating chronic HBV infection in children has been reported.[43] In a randomized, placebo-controlled trial, adefovir was more effective than placebo in children age ≥12 years at suppressing viral replication and normalizing transaminases.

### Tenofovir Disoproxil Fumarate (Tenofovir)

Tenofovir is a nucleotide analog structurally similar to adefovir that reduces HBV DNA levels in adults with lamivudine-resistant and wild-type HBV infection. A study in HIV/HBV-coinfected adults receiving stable cART comparing treatment with tenofovir or adefovir found similar efficacy in suppression of HBV DNA with no difference in toxicity.[70] Another study of HIV/HBV-coinfected adults receiving tenofovir in addition to lamivudine as part of their ARV regimen found that HBV DNA became undetectable in 30% of HBeAg-positive and 82% of HBeAg-negative patients, most of whom had lamivudine-resistant HBV infection.[59] As noted earlier, tenofovir is not approved for treatment of HBV infection in children aged <12 years, but tenofovir is approved as part of cART for HIV beginning at age 2 years.

However, for HIV/HBV-coinfected children aged ≥2 years who require treatment of both infections, tenofovir in combination with an anti-HBV nucleoside (either lamivudine or emtricitabine) can be considered **(BIII)**; a combined formulation of emtricitabine and tenofovir (Truvada) is available for adults. As with lamivudine and emtricitabine, tenofovir should not be used to treat chronic HBV in HIV-coinfected patients who are not receiving cART for HIV because of the risk of HIV-associated resistance mutations **(CIII)**.

### Entecavir

Entecavir is an oral nucleoside analogue that inhibits HBV DNA polymerase. When compared to lamivudine, entecavir therapy results in greater HBV viral suppression, increased normalization of serum transaminase levels, improved liver histology, and lower HBV resistance rates.[71] HBV viral suppression also has been demonstrated in HIV/HBV-coinfected adults. Entecavir treatment is approved for treatment of chronic HBV in adults and is preferred for lamivudine-resistant HBV infections. However, it recently was demonstrated to have suppressive activity against HIV.[72] Entecavir should not be used in HIV/HBV-coinfected patients who are not receiving cART for HIV. Entecavir is approved for use in children aged ≥16 years; no data are available on safety and efficacy of entecavir in younger children.

### Telbivudine

Telbivudine is a thymidine nucleoside analogue that was approved to treat chronic HBV in adults. It is well tolerated, but like lamivudine, resistance emerges over time, and telbivudine is not active against lamivudine-resistant HBV. No data are available on telbivudine in HIV/HBV-coinfected adults. Telbivudine is approved for use in children aged ≥16 years; no data are available on safety and efficacy of entecavir in younger children.

## *Duration of Therapy*

The optimal duration of therapy in HIV/HBV-coinfected children is not known. The duration of IFN-α treatment in HIV-uninfected children with chronic HBV infection is 6 months. At least 1 year of lamivudine therapy is recommended for HIV-uninfected children who have chronic HBV infection, with continuation of medication for ≥6 months after documented HBeAg seroconversion.[46] The duration of IFN therapy in HIV-infected children with HBV infection in whom treatment is indicated should be at least 6 months **(CIII)**. Among HBeAg-positive children who are HIV-uninfected, treatment of chronic HBV infection with antivirals should be continued until HBeAg seroconversion has been achieved and ≥6 months of additional treatment has been completed after the appearance of anti-HBe **(BI*)**.

However, because lamivudine (or emtricitabine) and tenofovir would be administered only to HIV/HBV-coinfected children who need HIV treatment and as part of a suppressive ARV regimen, treatment with lamivudine (or other anti-HBV drugs with anti-HIV activity) should be continued indefinitely in children with HIV/HBV coinfection, even if HBeAg seroconversion occurs **(CIII)**.

## *Monitoring and Adverse Events (Including IRIS)*

The parameters for successful therapy for chronic HBV infection are not well defined, but markers of improvement include decreased hepatic necroinflammatory disease, normalization of serum transaminase levels, reduction of HBV DNA levels, and HBeAg seroconversion. In children starting treatment for chronic

HBV infection, serum transaminase levels should be measured frequently at the start of therapy and then every 3 to 6 months. In children who are also beginning cART, some experts would monitor transaminase levels more frequently during the first few months of therapy (e.g, monthly for 3 months) because of the risk of IRIS (see below). Monitoring of response to treatment for chronic HBV infection is based on testing for HBV DNA and HBeAg and anti-HBe antibody on the same schedule as transaminase evaluations (every 3–6 months).

Close monitoring for relapse is needed after withdrawal of therapy. In patients who are HBeAg-negative, treatment should be continued until HBsAg clearance has been achieved **(BII)**.

In HIV/HBV-coinfected patients starting cART, serum transaminase elevations (flares) can occur as part of IRIS or secondary to cART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune-mediated, and restoration of immunocompetence with ARV treatment may reactivate liver inflammation and damage. Initiation of cART without anti-HBV therapy can lead to re-activation of HBV. This does not represent a failure of cART but rather a sign of immune reconstitution. IRIS manifests by an increase in serum transaminase levels as the CD4 cell count increases during the first 6 to 12 weeks of cART. Thus, serum transaminase levels should be monitored closely after introduction of cART. In such situations, cART should be continued and treatment for HBV infection initiated. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to cART in terms of immune reconstitution, and perhaps, improved survival. In patients experiencing hepatic flare, differentiating between IRIS and drug-induced liver toxicity may be difficult, and no reliable clinical or laboratory predictor exists to distinguish between the two. Close collaboration of the HIV specialist with a specialist in hepatic disease is recommended for such patients; a hepatologist should be consulted promptly if elevated aminotransferases levels are associated with clinical jaundice or other evidence of liver dysfunction (e.g., serum albumin).

Clinical and laboratory exacerbations of hepatitis and hepatic flare also can occur in coinfected children receiving cART if agents with anti-HBV activity are discontinued. Generally, once ARV drugs with anti-HBV activity are begun in coinfected children, they should be continued indefinitely unless contraindicated **(CIII)**. If discontinuation of therapy for chronic HBV infection results in hepatic flare, therapy for chronic HBV should be re-instituted **(BIII)**.

Some clinicians recommend monitoring HBV-infected children or adolescents for HCC with baseline screening and then annual or twice yearly determinations of serum alpha-fetoprotein (AFP) levels and abdominal ultrasonography; however, no data support the benefit of such surveillance.[3,38,46,47] Current recommendations in HBV-infected, HIV-uninfected adults support abdominal ultrasonography in men aged >40 years and women aged >50 years. The use of AFP monitoring is controversial.

Adverse effects of IFN-α use in children, although frequent, usually are not severe or permanent; however, approximately 5% of children require treatment discontinuation. The most common side effects include an influenza-like syndrome, cytopenias, and neuropsychiatric effects. Influenza-like symptoms comprising fever, chills, headache, myalgia, arthralgia, abdominal pain, nausea, and vomiting are seen in 80% of patients during the first month of treatment. These side effects decrease substantially during the first 4 months of therapy; premedication with acetaminophen or ibuprofen may reduce side effects. Subtle personality changes, which resolve when therapy is discontinued, have been reported in 42% of children.[40] Depression and suicidal ideation also have been reported in clinical trials of children treated with IFN-α.[73] Ophthalmologic complications have been reported in clinical trials of children with pegylated IFN.[74] Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypothyroidism or hyperthyroidism) have been reported with IFN-α therapy.[75] Loss of appetite with transient weight loss and impaired height growth can occur but usually resolves after completion of therapy.[76] Less commonly observed side effects of IFN-α include epistaxis and transient mild alopecia. Antinuclear auto-antibodies have been detected in some children treated with IFN-α.

IFN-α therapy is contraindicated in children with decompensated liver disease; severe cytopenia; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease **(CIII)**.[77]

Elevation of serum transaminase levels has been reported during IFN-α therapy in children and adults but usually is not an indication to stop therapy; these flares may herald impending HBeAg seroconversion.[46] Children receiving IFN-α therapy should be monitored with frequent complete blood count and liver function tests, and serum level of thyroid-stimulating hormone should be determined at baseline and periodically (e.g., at least every 3 months) for the duration of treatment.

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

## *Managing Treatment Failure*

Treatment failure is defined as ongoing HBV replication, persistent serum transaminase elevations, and the failure of HBeAg seroconversion in HBeAg-positive patients at the completion of therapy (for IFN) and after an adequate trial of oral anti-HBV antivirals (generally at least 6–12 months). In individuals with HBeAg-negative hepatitis, treatment failure is defined as ongoing HBV replication (>10,000 IU) and persistent serum transaminase elevations. Flares of liver disease with increasing HBV DNA levels can be seen with the development of resistance to lamivudine or emtricitabine.

In some children who have received initial treatment for chronic HBV infection with standard-dose IFN-α monotherapy, use of higher-dose IFN-α for retreatment improves response.[58,78,79]

Lamivudine also has been used as secondary therapy for young (<12 years old) HIV-uninfected children who have not responded to standard IFN-α therapy **(BI)**;[80-82] in HIV-infected children, initiation of a lamivudine-containing or emtricitabine-containing cART regimen (that also contains tenofovir, if aged ≥2 years) can be considered **(CIII)**.

For HIV/HBV coinfected children who develop lamivudine resistance during therapy, treatment options are more limited because of lack of data on use of adefovir, entecavir, and tenofovir for treatment of HBV infection in young children. Because these HBV drug-resistant isolates may have lower replicative capacity than wild-type HBV, some experts recommend continuing lamivudine or emtricitabine therapy in such cases **(CIII)**.

Alternatively, adding IFN-α can be considered or, in children old enough to receive adult doses of adefovir, adding that drug to the regimen can be considered **(CIII)**.

## *Preventing Recurrence*

Not applicable.

## *Discontinuing Secondary Prophylaxis*

Not applicable.

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## Dosing Recommendations for Prevention and Treatment of HBV in HIV/HBV Coinfected Children

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| Preventive Regimen | | | |
|---|---|---|---|
| **Indication** | **First Choice** | **Alternative** | **Comments/Special Issues** |
| **Primary Prophylaxis** | • Hepatitis B vaccine<br>• Combination of hepatitis B immunoglobulin and hepatitis B vaccine for infants born to mothers with hepatitis B infection | Hepatitis B immunoglobulin following exposure | See Figures 1 and 2 for detailed vaccine recommendations.<br>Primary Prophylaxis Indicated for:<br>• All individuals who are not HBV infected<br>Criteria for Discontinuing Primary Prophylaxis:<br>• N/A<br>Criteria for Restarting Primary Prophylaxis:<br>• N/A |
| **Secondary Prophylaxis** | Hepatitis A Vaccine | N/A | Secondary Prophylaxis Indicated for:<br>• Chronically HBV-infected individuals to prevent further liver injury<br>Criteria for Discontinuing Secondary Prophylaxis:<br>• N/A<br>Criteria for Restarting Secondary Prophylaxis:<br>• N/A |
| **Treatment** | Treatment of Only HBV Required (Child Does Not Require cART):<br>• IFN-α 3 million units/m$^2$ body surface area SQ 3 times a week for 1 week, followed by dose escalation to 6 million units/m$^2$ body surface area (max 10 million units/dose), to complete a 24-week course, or<br>• For children aged ≥12 years, adefovir 10 mg by mouth once daily for a minimum of 12 months (uncertain if risk of HIV resistance)<br>Treatment of Both HIV And HBV Required (Child Not Already Receiving 3TC or FTC)<br>• 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive cART regimen | • IFN-α 10 million units/m$^2$ body surface area SQ 3 times a week for 6 months (sometimes used for retreatment of failed lower-dose interferon therapy)<br>• Alternative for 3TC: FTC 6 mg/kg body weight (maximum 200 mg) once daily | Indications for Treatment Include:<br>• Detectable serum HBV DNA, irrespective of HBeAg status, for >6 months; and<br>• Persistent (>6 months) elevation of serum transaminases (≥ twice the upper limit of normal); or<br>• Evidence of chronic hepatitis on liver biopsy<br>IFN-α is contraindicated in children with decompensated liver disease; significant cytopenias, severe renal, neuropsychiatric, or cardiac disorders; and autoimmune disease.<br>Choice of HBV treatment options for HIV/HBV-co-infected children depends upon whether concurrent HIV treatment is warranted.<br>3TC and FTC have similar activity (and have cross-resistance) and should not be given together. FTC is not FDA-approved for treatment of HBV.<br>Tenofovir is approved for use in treatment of HIV |

**Dosing Recommendations for Prevention and Treatment of HBV in HIV/HBV Coinfected Children**
(page 2 of 2)

| Preventive Regimen | | | |
|---|---|---|---|
| **Indication** | **First Choice** | **Alternative** | **Comments/Special Issues** |
| **Treatment** | • For children aged ≥2 years, include tenofovir as part of cART regimen with 3TC or FTC. For children aged ≥12, tenofovir dose is 300 mg once daily. For children aged <12 year, and 8 mg/kg body weight per dose once daily (maximum dose 300 mg)<br><br><u>Treatment of Both HIV and HBV Required (Child Already Receiving cART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance)</u>:<br>• For children aged ≥2 years, include tenofovir as part of cART regimen with 3TC or FTC. For children aged ≥12 years, tenofovir dose is 300 mg once daily. For children aged <12 years, 8 mg/kg body weight per dose once daily (maximum dose 300 mg)<br>• For children aged ≥12 years, add adefovir 10 mg by mouth once daily or entecavir 0.5 mg by mouth once daily in addition to cART regimen.<br>• For children aged <12 years, give 6-month course of IFN-α as above in addition to cART regimen. | | infection in children aged ≥2 years but it is not approved for treatment of HBV infection in children aged <12 years. It should only be used for HBV in HIV/HBV-infected children as part of a cART regimen.<br><br>Adefovir is approved for use in children aged ≥12 years.<br><br>ETV is not approved for use in children younger than age 16 years, but is under study in HIV-uninfected children for treatment of chronic hepatitis B. Can be considered for older HIV-infected children who can receive adult dosage. It should only be used for HBV in HIV/HBV-infected children who also receive an HIV-suppressive cART regimen.<br><br>IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6 to 12 weeks of cART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS.<br><br>In children receiving tenofovir and 3TC or FTC, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HIV/HBV therapy has begun, it should be continued unless contraindicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation.<br><br>If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening.<br><br>Telbivudine has been approved for use in people aged ≥16 years with HBV; there are no data on safety or efficacy in children aged <16 years; a pharmacokinetic study is under way in HIV-uninfected children. |

**Key to Acronyms:** 3TC = lamivudine; cART = combined antiretroviral therapy; CD4 = CD4 T lymphocyte; FTC = emtricitabine; HBeAg = hepatitis B antigen; HBV = hepatitis B virus; IFN-α = interferon alfa; IRIS = immune reconstitution inflammatory syndrome; SQ = subcutaneous; tenofovir = tenofovir disoproxil fumarate

# 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*

***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*

## Epidemiology

In the United States, the prevalence of hepatitis C virus (HCV) infection is 0.2% among children aged 1 to 11 years and 0.4% among adolescents aged 12 to 19 years.[1,2] Modeling based on a recent U.S. census predicts that ~7,200 new cases of pediatric HCV infection occur annually.[3] At least six HCV genotypes are known (genotypes 1–6), with genotype 1 occurring most commonly in the United States.[4] The prevalence of HCV infection among HIV-infected children may be higher. In a serostudy of 535 HIV-infected children followed in pediatric HIV clinical trials, the prevalence of HCV infection by HCV antibody and RNA testing was 1.5%.[5] In a more recent study of 228 HIV-infected children at an inner-city hospital in the Bronx, seven HIV-infected children had chronic HCV infection (3.1% [95% CI, 1.4%–6.5%]), defined as a reactive HCV antibody and positive HCV real-time polymerase chain reaction (PCR).[6] The mean age of HIV/HCV-coinfected children was 16 years, and 57% had mild elevation (up to twofold above upper limit of normal) in serum transaminase levels.

Mother-to-child transmission (MTCT) is the predominant mode of HCV acquisition in children.[7,8] Other potential sources of HCV infection in older children, as for adults, include injection-drug use and, to a lesser extent, non-commercial body piercing or tattoos, unintentional needle stick injury, household contact, and sexual exposure.[9,10] Before 1992, blood transfusion was a source of HCV infection in children. A recent retrospective study found that 3% of infants who had received blood transfusions in a neonatal intensive-care unit between 1975 and1992 were anti-HCV-antibody positive.[11] However, the incidence of HCV infection from transfusion has dramatically declined since 1992, when second-generation HCV enzyme-linked immunosorbent assay (EIA) screening was implemented. With the current additional use of nucleic acid amplification testing, the risk of HCV infection through transfusion is approximately 1 in 2 million.[12]

The overall risk for MTCT of HCV from a woman infected with HCV alone ranges from 4% to 10%.[7,13-21] The primary risk factor for perinatal HCV transmission is maternal HCV viremia at delivery, although an absolute threshold for HCV transmission has not been identified.[14,22-27] Data do not indicate that HCV genotype is related to risk of perinatal HCV transmission.[14,20] Although a few studies have suggested that vaginal delivery increases risk of HCV transmission[13,15,17,22] and that HCV can be transmitted during the intrapartum period,[28] most studies have found that mode of delivery does not appear to influence perinatal HCV transmission.[8,15,16,18,29-33] In addition, even though HCV RNA can be detected in breast milk, studies of infants born to HCV-infected women have not demonstrated a higher risk of HCV transmission in breastfed infants than in those who are formula-fed.[8,13-16,18,25,28,29,34]

Maternal HIV coinfection increases the risk of perinatal transmission, with perinatal HCV transmission rates of 6% to 23% reported for infants born to women who are HIV/HCV-coinfected[7,13-15,19,26,30-32,35-41] Furthermore, a few studies suggest that children who are infected with HIV during the perinatal period may be more likely than HIV-uninfected children to acquire HCV infection from mothers who are HIV/HCV-coinfected.[30,31,38,40] Dual virus transmission has been reported in 4% to 10% of children born to HIV/HCV-coinfected mothers.[13,30,36,38,39] HCV RNA levels are hypothesized to be higher among women coinfected with HIV than in those infected with HCV alone, which could account, in part, for the increased risk of MTCT of HCV from HIV/HCV-coinfected women; however, not all studies have found higher levels of HCV viremia among HIV-infected mothers.[24,31,35] One European study suggested that perinatal transmission of HCV may be reduced in HIV-infected women receiving combination antiretroviral therapy (cART).[32]

Acute HCV infection appears to spontaneously resolve in 15% to 25% of adults.[4] Findings from a limited number of longitudinal studies suggest that HCV infection resolves spontaneously in 17% to 59% of children with perinatal HCV infection.[42-47] Spontaneous viral clearance in perinatal HCV infection was more common with HCV genotype 3 and usually occurred by age 3 years.[46,48] Spontaneous viral clearance also has been associated with the presence of CC interleukin-28 (IL28B) host genotype in perinatally HCV-infected infants.[49]

Chronic HCV infection is defined as the presence of HCV RNA for >6 months. A study from Italy reported on long-term outcome in more than 350 children with chronic, untreated HCV infection (mean follow up 5.9±3.8 years), encompassing both perinatal and parenteral modes of transmission. The overall proportion of children who had spontaneous viral clearance was 7.5%. The rate of spontaneous viral clearance in the vertically acquired cases was 11.5%: half of these cases were genotype 3 and clearance occurred within the first 3 years of life. Evidence of chronic liver disease and cirrhosis was present in 1.8% of HCV-infected children. The average time from diagnosis of HCV infection to development of cirrhosis was 9.87±5.9 years.[50] In a study comparing children with perinatal HIV/HCV coinfection with those with perinatal HCV infection alone, spontaneous clearance of HCV infection occurred in 10 (17.5%) of 57 with HCV monoinfection but none of the 13 children with HIV/HCV coinfection.[51]

## Clinical Manifestations

Children with perinatal HCV infection appear to have a more benign clinical course than do adults with newly acquired HCV infection.[9,52,53] Most HCV-infected children are asymptomatic, with minor abnormalities such as hepatomegaly, or mild nonspecific symptoms such as fatigue, myalgias, and poor weight gain;[9,53,54] however, intermittent asymptomatic elevations in transaminase levels are common during the first 2 years of life.[45,54-56] In a large European cohort of HCV-infected children, about 20% of children had apparent clearance of HCV viremia; 50% had chronic asymptomatic infection, characterized by intermittent viremia, rare hepatomegaly, and usually normal liver transaminase levels; and 30% had chronic active infection with persistent viremia and abnormal transaminase levels.[46]

Histopathologic inflammatory changes of chronic hepatitis may be present in patients with chronic HCV infection despite lack of symptoms, normal serum transaminase levels, and low HCV RNA levels.[54] Analysis of liver histology in 121 treatment-naive pediatric patients showed some degree of inflammation in all samples, mild fibrosis (Ishak stage 1–2) in 80% and cirrhosis in only 2% of patients.[57] Most children with chronic HCV infection who have undergone liver biopsy and are included in published studies typically have mild-to-moderate liver disease as determined by signs of structural alterations, inflammatory activity, and necrosis.[9,24,53,55] Similar proportions of vertically and parenterally HCV-infected children have signs of chronic hepatitis on liver biopsy.[56] A small subset of children may develop severe liver disease. In a study of 60 children with perinatally acquired or transfusion-acquired HCV infection who were infected for a mean duration of 13 years, 12% had significant fibrosis on liver biopsy.[53] Older age at time of infection and elevated serum gamma-glutamyltranspeptidase correlated with fibrosis; serum transaminase levels correlated with inflammation.[53]

In HIV/ HCV-coinfected adults, the natural history of HCV infection appears to be accelerated, with more rapid progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), and death.[58,59] In HIV/HCV-coinfected adults, there are conflicting reports about the effect of cART and immune reconstitution on liver-related mortality, with some studies showing decreases and others little difference in liver-related mortality.[60,61] Data are minimal on the effect of HIV/HCV-coinfection on the natural history of HCV infection in children and insufficient to draw conclusions about HCV disease progression in coinfected children.[7]

Data are conflicting on the impact of HCV infection on HIV disease progression in adults; some studies suggest higher rates of HIV progression and others do not.[7] The effect of pediatric coinfection on HIV disease progression also is unclear because the number of coinfected children is small, and few studies have evaluated this. Two studies of children with perinatal HIV/HCV coinfection found no increase in HIV progression. On the other hand, in a study from Spain comparing children with perinatal HIV/HCV coinfection with those with perinatal HCV infection alone, HCV viremia and maximum transaminase levels were higher in the coinfected children than in those with HCV infection alone.[51] In a study of older children with thalassemia who were infected through transfusion, disease progression was more rapid and mortality higher in those with HIV/HCV-coinfection than in those with HIV monoinfection.[30,39,62]

## Making the Diagnosis

Testing for HCV infection should be performed on any child whose mother is known to have HCV infection **(AIII)**. All HIV-infected adults and adolescents should be tested for HCV infection **(AIII)**.

Serologic and nucleic acid tests are used to diagnose HCV infection. HCV RNA first becomes detectable 1 to 3 weeks after HCV infection and precedes serologic response to HCV.[4] A third-generation EIA is available for detecting antibody to HCV (anti-HCV). Passively transferred maternal anti-HCV can be detected for up to 18 months in infants born to HCV-infected mothers. In a large cohort of HCV-exposed but -uninfected children, anti-HCV was present in 15% of children at 12 months, 5% at 15 months, and 2% at 18 months.[24] Therefore, only the presence of persistent HCV viremia can be used to reliably verify HCV infection in at-risk children aged <18 months.[63] HCV infection can be diagnosed in such children using a nucleic acid test to detect HCV RNA after age 1 month; the sensitivity of the HCV RNA testing is low at birth (22%), but increases to 85% at 6 months.[64] Most children with perinatal HCV infection will have a positive HCV RNA test by age 12 months. However, because of intermittent viremia, a single negative HCV RNA test is not conclusive evidence of lack of infection. Thus, two negative HCV RNA results obtained at or after age 2 months, including at least one test at or after age 12 months, definitively excludes HCV infection in an HCV-exposed infant **(BIII)**. Two positive HCV RNA results before age 18 months are required for definitive diagnosis of HCV infection **(BIII)**.[64]

A positive anti-HCV antibody test in a child aged >18 months indicates prior HCV infection. Supplemental testing with a more specific assay, such as HCV RNA testing, is recommended to clarify whether the positive antibody test indicates a chronic active or a resolved infection **(AIII)**. A positive HCV RNA test confirms current HCV infection, and if positive for >6 months, indicates chronic infection. HCV RNA can be measured qualitatively or quantitatively. Qualitative nucleic acid tests include qualitative PCR and transcription-mediated amplification. Quantitative tests include branched-chain DNA amplification, quantitative PCR, and real-time PCR and are most useful for monitoring response to anti-HCV therapy. Quantitative HCV RNA level (i.e., HCV viral load) does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important information about response to antiviral therapy. Assays vary substantially, and if serial values are required to monitor treatment, continued use of the same quantitative assay for all assessments is strongly recommended.

Liver biopsy is the most accurate test to assess the severity of hepatic disease and measure the amount of hepatic fibrosis present. The degree of liver injury found on biopsy can be used to determine the need for treatment. A liver biopsy is recommended before initiating therapy for chronic HCV genotype 1 infection, but is often used for other genotype infections (2, 3 or 4) as well.[65,66] Virus eradication from anti-HCV therapy is much more likely in HCV genotypes 2 and 3 (~80%), compared with genotype 1 (<50%). Thus, the need for liver biopsy before treatment of HCV genotypes 2 or 3 is debatable.[67]

## Prevention Recommendations

### *Preventing Exposure*

All HIV-infected patients should be screened for HCV. No reliable strategy exists to prevent perinatal HCV transmission. Cesarean delivery is not associated with reduced perinatal transmission of HCV infection and is not recommended for this purpose for women with chronic HCV infection **(AII)**. The presence of maternal HCV coinfection does not alter the current recommendation for scheduled cesarean delivery for HIV-infected women who have HIV RNA levels >1,000 copies/mL near delivery to prevent perinatal HIV transmission. Limited data suggest that breastfeeding does not transmit HCV; maternal HCV infection is not a reason to avoid breastfeeding. The presence of maternal HCV coinfection does not alter the current recommendation that HIV-infected women in the United States should not breastfeed their infants (see *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*).

No vaccines are available to prevent HCV infection. Adolescents considering tattooing or body-piercing should be informed about potential risks of acquiring HCV, which could be transmitted if equipment is not sterile or if proper infection-control procedures are not followed, and to avoid injection-drug use and unprotected sex **(BIII)**.[68] HCV-infected persons should be advised not to share toothbrushes, razors, tweezers, nail clippers and other personal-care articles that might be contaminated with blood to prevent transmission of HCV.

### *Preventing First Episode of Disease*

Patients with chronic liver disease can develop fulminant hepatitis from hepatitis A (HAV) or B (HAB) infection; all children (regardless of HIV and HCV infection status) should receive standard vaccination with HAV and HAB vaccines **(AIII)**.[68-70] Patients with advanced HCV-related liver disease and/or HIV infection may not mount an appropriate immune response to vaccines.[71] Therefore, measurement of HBV antibody titers 3 months after completion of the vaccination series is recommended.[72]

## Treatment Recommendations

### *Treating Disease*

The standard of care for treatment of chronic HCV infection in children, in the absence of HIV infection, is combination therapy with pegylated interferon-alfa (Peg-IFN-α) administered as a subcutaneous (SQ) injection once a week and twice-daily oral ribavirin.[73] For HIV-uninfected individuals, the length of therapy is 48 weeks for treating HCV genotype 1, and 24 weeks for genotypes 2 or 3. Recent studies demonstrate improved response rates in adults with the addition of protease inhibitors (PIs) (telaprevir or boceprevir) to pegylated-IFN-α and ribavirin in adults with HCV genotype 1 infection.[74,75] A recently completed randomized, double-blind, placebo-controlled trial of peg-IFN-α with and without ribavirin in HCV-infected children has shown superior efficacy with combination therapy.[76] Improved viral eradication was previously noted with combination therapy in a non-randomized European study as well.[67] There is a paucity of studies on the treatment of HIV/HCV-coinfected children. Consultation with experts in treating chronic HCV infection in children is recommended.

The PIs telaprevir and boceprevir have been approved for use in adults for treatment of HCV genotype 1, in concert with peg-IFN-α and ribavirin therapy.[77] This "triple therapy" was associated with markedly improved viral clearance, with sustained virologic responses demonstrated in up to 68% of treated patients.[75]

### *HIV/HCV-coinfected Adults and Adolescents*

Regardless of HIV coinfection status, treatment should be considered in all non-pregnant, HCV-infected adults or adolescents who have abnormal serum transaminase levels and liver biopsies that show chronic hepatitis with inflammation, fibrosis, and compensated liver disease.[78] Because of the high rate of HCV eradication with treatment for HCV genotypes 2 or 3, a liver biopsy is optional before initiating therapy. Treatment should be considered for HIV/HCV-coinfected adults and adolescents for whom potential benefits of treatment are judged to outweigh potential risks, including those infected with HCV genotypes 2 or 3, those with stable HIV infection not requiring cART, and those with HCV-related cryoglobulinemic vasculitis or glomerulonephritis.[65,79] Baseline serum HCV RNA level and HCV genotype are the primary predictors of response to treatment. Younger age, higher CD4 T lymphocyte (CD4 cell) count, elevated transaminase levels, lack of liver fibrosis, low body mass index, lack of insulin resistance, and white race are other variables associated with better treatment response.[79] The recommended treatment for HCV genotypes 2 and 3 is combined peg-IFN-α2a (or 2b) plus ribavirin for 48 weeks, while telaprevir is added to that regimen for the first 12 weeks in most adults with HCV genotype 1 infection (see *Adult OI Guidelines*). In HIV/HCV-coinfected adults, rates of sustained virologic response to treatment with peg-IFN-α plus ribavirin range from 44% to 73% for treatment of HCV genotypes 2 and 3 infection and from 14% to 29% for HCV genotype 1 infection.[73,80,81] Response to anti-HCV treatment improves in HIV/HCV-coinfected adults with CD4 cell counts >200 cells/mm$^3$; therefore, cART should be considered before anti-HCV therapy is initiated in HIV/HCV-coinfected patients with CD4 cell counts <200 cells/mm$^3$. Anti-HCV treatment is not recommended during pregnancy for HCV-infected women because ribavirin is teratogenic.

### *HCV-Infected, HIV-Uninfected Children*

Treatment usually is not recommended for HIV-uninfected children aged <3 years who have HCV infection because spontaneous HCV clearance can occur in this age group **(BIII)**. All decisions about treatment of HCV infection in children should be individualized because HCV usually causes mild disease in this population and few data exist to identify risk factors differentiating those at greater risk for progression of liver disease.[80,82]

HCV-infected, HIV-uninfected children ≥3 years old who are chosen for treatment should receive combination therapy with peg-IFN-α and ribavirin for 48 weeks for genotype 1 and 24 weeks for genotypes 2 or 3 **(AI)**. This recommendation is based on the results of a recently completed pediatric trial in the United States on the efficacy of peg-IFN-α with or without ribavirin.[76] In this trial, children aged 5 to 17 years were defined as having chronic HCV infection based on at least 2 positive HCV RNA blood tests for >6 months duration and liver histology consistent with HCV infection. The primary outcome measured was a sustained virologic response (SVR) defined as non-detectable HCV RNA in plasma at 24 weeks after treatment completion. The overall SVR was 53% with combination therapy and 21% with peg-IFN-α monotherapy. Combination therapy resulted in SVR in 47% of patients with genotype 1 HCV and 80% of patients with genotypes 2-6 HCV. A non-randomized trial using peg-IFN-α and ribavirin for pediatric HCV infection in Europe found similar efficacy for combination therapy. SVR was achieved in 48% of patients with genotype 1 and 100% of patients with genotypes 2 or 3.[67]

Previous studies on the use of combination therapy with standard IFN-α (SQ injections 3 times weekly) and ribavirin reported overall rates of SVR ranging from 46% to 65%.[66,83-87] In these studies, children infected with genotype 1 were less likely to have a SVR (36%) than those infected with genotypes 2 or 3 (SVR 84%).[83] Other factors associated with favorable response to anti-HCV treatment in children include lower pretreatment HCV RNA levels, white race, and possibly younger age.[66]

## *HIV/HCV-coinfected Children*

No specific studies have been done of treatment of children with HIV/HCV-coinfection, and recommendations are based primarily on data from adults. Because therapy for HCV infection is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected children aged ≥3 years who have no contraindications to treatment **(BIII)** (see Dosing Table for contraindications to anti-HCV drugs). Treatment of HIV/HCV-coinfected children aged <3 years usually is not recommended **(BIII)**, even though spontaneous HCV clearance in HIV/HCV-coinfected children may occur at lower rates than in HIV-uninfected children.[51]

In HIV/HCV-coinfected adults, the recommended duration of combination treatment is 48 weeks for infections with all HCV genotypes, including 2 and 3, because coinfected adults may not respond as well as those who are HIV-uninfected and they may have higher rates of relapse. Moreover, the efficacy of shorter treatment has not been adequately evaluated in HIV-infected individuals.[79] By extrapolation, 48 weeks of therapy also are recommended for HIV/HCV-coinfected children, regardless of genotype **(BIII)**. Potential drug interactions complicate the concomitant use of cART and anti-HCV therapy. Ribavirin enhances phosphorylation of didanosine, which could increase the risk of toxicity; therefore, these drugs should not be used together **(AIII)**. Ribavirin and zidovudine both are associated with anemia and should not be administered together **(BII*)**.[79]

The PIs telaprevir and boceprevir are approved only for use in adults with genotype 1 HCV infection. These agents may be tested and approved for use in children in the near future. No recommendations for use of these agents in children can be made at this time. See *Adult OI Guidelines* for important warnings about drug interactions between HCV PIs and HIV PIs and other antiretroviral drugs.

## *Monitoring and Adverse Events (Including IRIS)*

### Monitoring in Children Not Receiving Anti-HCV Therapy

Although no evidence-based long-term monitoring guidelines exist for children with perinatally acquired HCV, many experts monitor HCV RNA levels and serum transaminase levels every 6 to 12 months and complete blood counts (CBC) and serum alpha fetoprotein levels annually.[82] Serum transaminase levels can fluctuate and do not necessarily correlate with histologic liver damage because significant liver disease can be present in patients with normal serum transaminase levels. In HCV-infected persons who are HIV-uninfected, HCC rarely is seen in the absence of cirrhosis. The benefits of serum alpha-fetoprotein (AFP) and abdominal sonography as screening tools for HCC have not been studied in children. Some experts perform periodic sonographic screening at defined intervals (every 2-5 years) in children with chronic HCV infection; others do these tests only in those with advanced liver disease and/or rising serum AFP concentrations.[82] The risk of HCC in HCV-infected children, with or without HIV infection, is unknown.

As with HIV/HBV-coinfection, use of cART in HIV/HCV-coinfected patients can worsen hepatitis, with increases in serum transaminase levels and clinical signs of liver disease, including hepatomegaly and jaundice (also called “hepatic flare”). This does not represent a failure of ART, but rather, is a sign of immune reconstitution. Immune reconstitution inflammatory syndrome (IRIS) manifests by an increase in serum transaminase levels as the CD4 cell count increases during the first 6 to 12 weeks of cART. Thus, serum transaminase levels should be monitored closely after introduction of cART in HIV/HCV-coinfected children. The prognosis for most patients with IRIS is favorable. Consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction, in other words, low serum albumin.

**Monitoring During Combination Therapy (Interferon and Ribavirin)**

HCV RNA quantitation is used to monitor response to antiviral therapy. HCV RNA levels should be performed at baseline; after 5, 12, and 24 weeks of antiviral therapy; at treatment completion (48 weeks); and 6 months after treatment cessation. Some experts continue to perform serial HCV RNA testing at 6- to 12-month intervals for an additional 1 to 5 years to exclude late virologic relapse.

The following are outcomes measured during the treatment of HCV:

- **Rapid Virological Response (RVR):** Non-detectable plasma HCV RNA after 4 weeks of therapy;
- **Early Virologic Response (EVR):** Decrease in HCV RNA ≥2 $\log_{10}$ IU/mL below baseline after 12 weeks of therapy;
- **End Of Treatment Virologic Response:** Non-detectable HCV RNA at time of treatment completion;
- **Sustained Virologic Response (SVR):** Non-detectable HCV RNA at 24 weeks after treatment completion;
- **Virologic Relapse:** Achievement of end of treatment response followed by return of HCV RNA positivity after treatment completion;
- **Nonresponse:** Failure to suppress HCV RNA below detection at any time during treatment; and
- **Breakthrough Response:** Reemergence of detectable HCV RNA from non-detectable status despite the continuation of therapy.[4]

In the absence of specific data for HIV/HCV-coinfected children, the criteria for determining response to therapy in HCV-monoinfected children and HIV/HCV-coinfected adults are used. Failure to achieve EVR with treatment with peg-IFN-α and ribavirin correlates with a low chance (<3%) of achieving SVR (based on adult data) and treatment can be discontinued after 12 weeks. Treatment should be discontinued in patients who achieve an EVR but still have detectable HCV RNA at 24 weeks of therapy. For all other HIV/HCV-coinfected children, treatment should be given for 48 weeks, regardless of genotype **(BIII)**. In addition to HCV RNA quantification, patients receiving antiviral therapy for HCV infection should be closely monitored for medication side effects with CBC, measurement of serum transaminase levels, thyroid function tests, ophthalmologic exams, and assessment of mental status/mood disorders. Some experts would monitor transaminase levels more frequently during the first few months of therapy, such as monthly for 3 months, in HIV/HCV-coinfected children who are also starting cART because of the risk of IRIS.

Side effects of IFN-α in children are common but usually not severe; approximately 5% of children need to discontinue treatment because of side effects. The most common side effects include influenza-like symptoms (e.g., fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, vomiting) in 80% of patients during the first month of treatment. However, these symptoms usually resolve over time and usually are not treatment-limiting; pre-medication with acetaminophen or ibuprofen may reduce the incidence of side effects. In 42% of children subtle personality changes that resolve when therapy is discontinued have been reported.[88] Depression and suicidal ideation also have been reported in clinical trials of children treated with IFN-α.[83] Neutropenia, which usually improves with dose-reduction, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypothyroidism or hyperthyroidism) have been reported with IFN-α therapy.[89] Loss of appetite, with transient weight loss and impaired height growth, can occur but usually resolves after completion of therapy.[90]

Less commonly observed side effects of IFN-α include epistaxis and transient mild alopecia. Some children develop antinuclear autoantibodies. The incidence of interferon-associated ophthalmologic complications in HCV-infected children on combination therapy was recently reported.[91] Three of 114 patients developed significant eye disease, including ischemic retinopathy with cotton wool spots, uveitis, and transient monocular blindness. Despite the low incidence of disease, the severity of the ophthalmologic findings warrants follow-up with eye exams at 24 and 48 weeks of therapy. IFN-α therapy is contraindicated in children with decompensated liver disease, substantial cytopenias, renal failure, severe cardiac or neuropsychiatric disorders, and non-HCV-related autoimmune disease **(AII*)**.[92]

Side effects of ribavirin include hemolytic anemia and lymphopenia. Ribavirin-induced hemolytic anemia is dose-dependent and usually presents with a substantial decrease in hemoglobin within 1 to 2 weeks after ribavirin initiation, but the hemoglobin usually stabilizes. Significant anemia (hemoglobin <10 g/dL) occurs in about 10% of ribavirin-treated children.[82] Erythropoietin can be used to manage clinically significant anemia during HCV treatment **(BIII)**. Coadministration of didanosine is contraindicated in children receiving ribavirin because this combination can increase the risk of mitochondrial toxicity and hepatic decompensation **(AIII)**. Children receiving concomitant zidovudine may be more likely to experience bone marrow suppression; if possible, zidovudine should be avoided in children receiving ribavirin **(BII*)**. Children who are receiving zidovudine and ribavirin together should be monitored closely for neutropenia and anemia. Ribavirin is teratogenic and should not be used by pregnant women. Sexually active adolescent girls or those likely to become sexually active who are receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy.

In patients on HCV therapy who start cART and experience hepatic flares, differentiating between IRIS and drug-induced liver toxicity may be difficult, and no reliable clinical or laboratory predictors exist to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease—usually a hepatologist—is recommended for such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (such as low serum albumin).

## *Managing Treatment Failure*

No data exist on which to base recommendations for treatment of HIV/HCV-coinfected children in whom initial HCV treatment fails. In HIV/HCV-coinfected adults, a second course of treatment has a limited chance of resulting in sustained virologic response in nonresponders (those who do not achieve early virologic response by week 12 or undetectable HCV load at week 24) or patients whose HCV relapses. Therapeutic interventions for such adults need to be individualized according to prior response, tolerance, and adherence to therapy; severity of liver disease; viral genotype; and other underlying factors that might influence response. Some experts might extend the duration of treatment (e.g., to 72 weeks) in adults who experience a virologic response followed by relapse after adequate HCV therapy or in patients with advanced fibrosis. In the setting of treatment failure, the addition of PIs (telaprevir or boceprevir) to peg-IFN-α and ribavirin may increase rates of eradication.[74,75] In a clinical trial, the addition of boceprevir to peg-IFN-ribavirin resulted in significantly higher rates of sustained virologic response (up to 66%) in previously treated adults with chronic HCV genotype 1 infection, as compared with peg-interferon-ribavirin alone.[93] HIV/HCV-coinfected adults with prior suboptimal treatment of HCV genotypes 2 or 3 infection may benefit from optimized retreatment; coinfected adults with treatment failure for HCV genotype 1 infection may benefit from retreatment with a combination regimen that includes boceprevir or telaprevir (see *Adult OI Guidelines*). See *Adult OI Guidelines* for important warnings about drug interactions between HCV PIs and HIV PIs and other antiretroviral drugs. No data exist on which to base a recommendation for management of HCV treatment failure in HIV/HCV-coinfected children, and pediatric trials of triple therapy are warranted.

### *Preventing Recurrence*

Not applicable.

### *Discontinuing Secondary Prophylaxis*

Not applicable.

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## Dosing Recommendations for Prevention and Treatment of Hepatitis C Virus (HCV)

| Preventive Regimen | | | |
|---|---|---|---|
| **Indication** | **First Choice** | **Alternative** | **Comments/Special Issues** |
| **Primary Prophylaxis** | None | N/A | N/A |
| **Secondary Prophylaxis** | None | N/A | N/A |
| **Treatment** | IFN-α Plus Ribavirin Combination Therapy:<br>• Pegylated IFN-α: Peg-IFN 2a 180 µg/1.73 m$^2$ body surface area subcutaneously once per week (maximum dose 180 µg) OR Peg-IFN 2b 60 µg/m$^2$ body surface area once per week<br>PLUS<br>• Ribavirin (oral) 7.5 mg/kg body weight twice daily (fixed dose by weight recommended):<br>• 25–36 kg: 200 mg a.m. and p.m.<br>• >36 to 49 kg: 200 mg a.m. and 400 mg p.m.<br>• >49 to 61 kg: 400 mg a.m. and p.m.<br>• >61 to 75 kg: 400 mg a.m. and 600 mg p.m.<br>• >75 kg: 600 mg a.m. and p.m.<br>Treatment Duration:<br>• 48 weeks, regardless of HCV genotype | None | Optimal duration of treatment for HIV/HCV-coinfected children is unknown and based on recommendations for HIV/HCV-coinfected adults<br>Treatment of HCV in children <3 years generally is not recommended.<br>Indications for treatment are based on recommendations in HIV/HCV-coinfected adults; because HCV therapy is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected children aged >3 years in whom there are no contraindications to treatment<br>For recommendations related to use of telaprevir or boceprevir in adults, including warnings about drug interactions between HCV protease inhibitors and HIV protease inhibitors and other antiretroviral drugs, see *Adult OI guidelines*.<br>IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6–12 weeks of cART. It may be difficult to distinguish between IRIS and drug-induced hepatotoxicity or other causes of hepatitis.<br>IFN-α is contraindicated in children with decompensated liver disease, significant cytopenias, renal failure, severe cardiac disorders and non-HCV-related autoimmune disease.<br>Ribavirin is contraindicated in children with unstable cardiopulmonary disease, severe pre-existing anemia or hemoglobinopathy.<br>Didanosine combined with ribavirin may lead to increased mitochondrial toxicities; concomitant use is contraindicated.<br>Ribavirin and zidovudine both are associated with anemia, and when possible, should not be administered together |

**Key to Acronyms:** cART = combined antiretroviral therapy; HCV = hepatitis C virus; IFN = interferon; IRIS = immune reconstitution inflammatory syndrome; Peg-IFN = pegylated interferon; SQ = subcutaneous

# 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?<br>• Condoms should be used to prevent HSV infection (and other sexually transmitted diseases) in adolescents and young adults with HIV (strong; low).<br>The data regarding the level of protection provided by condoms are very limited for individuals with HIV in general, and for youth specifically.<br>**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)?<br>• 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).<br>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)?<br>• 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).<br>**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)?<br>• 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).<br>**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?**<br>• 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<br>*Strength of Recommendation:* Strong; Weak<br>*Quality of Evidence:* High; Moderate; Low; or Very Low |

## Epidemiology

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) can cause disease at any age. It is generally regarded that HSV-1 is transmitted primarily through contact with infected oral secretions and that HSV-2 is acquired primarily through contact with infected genital secretions. However, among some populations of older adolescents and young adults, HSV-1 is the cause of a large proportion of first episodes of genital HSV infection.[1-4] In the United States, HSV-1 seroprevalence reaches 30% by adolescence.[5-7] Seroprevalence is higher among children who live below the poverty level and in non-Hispanic black children and children born in Mexico or of Mexican heritage.[5,6] The seroprevalence of HSV-1 approaches 60% in older adults. HSV-2 seroprevalence before reported onset of sexual activity is low (approximately 2%); rises to 20% to 26% in adults 30 to 49 years, and is higher in non-Hispanic blacks, individuals with multiple sex partners and early age of onset of sexual activity, females, and in those living below the poverty level.[6,7] Among young adolescent girls, a longer history of sexual activity and another sexually transmitted disease in the past 6 months was associated with HSV-2 seropositivity.[8] These epidemiologic data indicate that children are at significant risk for primary infection or reactivation with HSV 1 and/or HSV-2 throughout childhood and adolescence. The age-specific seroprevalence of both HSV types is higher in many developing countries.[9-11]

Young children generally acquire HSV-1 from the oral secretions of caretakers or playmates. Rarely is this the result of contact with active herpetic lesions; infection most often results from exposure to HSV shed asymptomatically in the saliva of the contact. Salivary shedding of HSV detected by polymerase chain reaction (PCR) in adults who are HSV-1-seropositive is frequent (9% to 30% of days).[12-14] Older individuals who avoided infection during childhood or adolescence also acquire HSV-1 (oral or genital) from exposure to infected saliva. HSV-2 is more likely to be acquired during adulthood or adolescence than in childhood as it is typically sexually transmitted. Genital shedding of HSV-2 by women who do not have HIV, as detected by PCR, is frequent (19% of days).[12] Either HSV type can be transmitted by oral-oral, oral-genital, and genital-genital contact. In general, shedding of oral HSV persists longer in young children. Oral and genital HSV shedding is more common in close proximity to the first episode of infection and in patients with HIV (30% of days in individuals who are HSV seropositive and not on antiretroviral therapy [ART]).[15,16]

HSV infection can be acquired as a neonatal infection, primarily through exposure to HSV-infected maternal fluids during vaginal delivery; less commonly, infection may occur *in utero*.[17,18] Newborns are infected infrequently from oral secretions of an adult caretaker. The risk of transmitting HSV during delivery is approximately 1% in pregnant women with remote primary HSV infection, whereas the risk is much higher for infants born to women with recent HSV infection (range: 30% to 50%).[18] Maternal HSV antibody status before delivery appears to reduce the probability of transmission to infants and the severity of neonatal infection.[19,20] Genital shedding of HSV at delivery and presence of a fetal scalp monitor electrode increase the risk of transmission, as does prolonged rupture of membranes (>6 hours), probably because of ascending HSV infection from the cervix. Importantly, mothers of neonates with active HSV disease often do not have a clinical history of either past genital HSV infection or incident genital lesions, as maternal infection is frequently asymptomatic.[21,22]

HSV co-infection in pregnant women with HIV is not uncommon because both viral infections share risk factors (race, socioeconomic status, and number of sexual partners). Genital HSV-2 was detected by PCR in 23% to 31% of HSV-seropositive women with HIV at the time of delivery, compared with 9% to 12% of HSV-seropositive pregnant women without HIV.[16,23] Shedding is greatest when the CD4 T lymphocyte (CD4) count is low and/or the patient is not receiving ART.[15,24] However, there is no evidence that *in utero* HSV infection of the fetus occurs more frequently in pregnant women with HIV/HSV-2 co-infection, or that infants born to these women are at increased risk of perinatal (intrapartum) HSV infection. In the general population, the neonatal HSV infection rate is 1 case per 2,000 to 10,000 deliveries, indicating that neonatal HSV will be observed rarely at clinics caring for co-infected pregnant women.[17,25]

Numerous studies have shown that co-infection with genital HSV-2 in adults is associated with higher titers of HIV RNA in plasma and genital secretions; HSV-2-seropositivity increases the risk of HIV transmission to sexual partners, even in the absence of genital ulcer disease.[26,27] Three studies suggest that maternal HSV-2 co-infection increases the risk of intrapartum HIV transmission.[28-30]

## Clinical Manifestations

In most immunologically competent children outside of the neonatal period, HSV infection causes minimal signs and symptoms and is often unrecognized as a distinct illness. Up to one third of all immunocompetent children may develop a characteristic orolabial syndrome (primary gingivostomatitis), usually from HSV-1 infection, which leads to fever, irritability, tender submandibular lymphadenopathy, and superficial, painful ulcers on the gingival and oral mucosa and perioral skin.[31,32] HSV viremia occurs in approximately one-third of patients with primary herpetic gingivostomatitis.[33] In addition, HSV is a common cause of severe posterior pharyngitis in older children and adolescents.[34,35] Children with advanced HIV infection may have primary infection with multiple lesions that are atypical in appearance and delayed in healing.[36] Very rarely, disseminated HSV with visceral involvement (including liver, adrenals, lung, and brain) and generalized skin lesions occurs in individuals with HIV.[37] A small number of recurrent perioral or perinasal vesicles ("cold sores" or "fever blisters") that heal quickly can occur intermittently in both healthy children and children with HIV throughout their lives, but those with AIDS are at risk of frequent recurrences, which can be associated with severe ulcerative disease and symptoms similar to primary HSV infection.[36,38] Children with HIV also may have prolonged shedding of HSV after both primary and reactivation infection. HSV esophagitis can occur in severely immunocompromised children. A study in adults found that patients with

HIV who have HSV esophagitis often lack evidence of oral HSV infection.[39] Prolonged cutaneous HSV infection and organ involvement are AIDS-indicator conditions. However, these illnesses are uncommon in children with HIV in the era of ART, with a documented incidence rate of systemic HSV of only 0.30 per 100 child-years.[40,41]

Genital infection is the most common manifestation of HSV-2 infection in sexually active adolescents. Most primary infections are asymptomatic or subclinical in adolescents who are not HIV infected. Symptomatic disease is characterized by painful, ulcerative lesions on the perineum, penis, labia, and vaginal/urethral mucosae. Mucosal disease often is accompanied by dysuria and/or vaginal or urethral discharge. Inguinal lymphadenopathy is common with perineal disease during primary infection.[42] Frequent recurrences and delayed healing are more likely in severely immunosuppressed patients. Severe HSV proctitis and perianal infections occur in, but are not limited to, patients who practice receptive anal intercourse.[43,44]

HSV keratitis and herpetic whitlow in patients with HIV are similar in presentation to these diseases in individuals without HIV, but may be more severe. Acute retinal necrosis and progressive outer retinal necrosis are rare sight-threatening complications that occur more frequently in immunocompromised individuals.[45,46] HSV encephalitis occurs in patients with HIV, but is not more frequent or more severe than in individuals without HIV and has similar signs and symptoms.[47,48]

Neonatal HSV infection in infants born to mothers with HIV and HSV is similar in presentation to that seen in infants of mothers with HSV alone. Neonatal HSV can appear as disseminated multiorgan disease, localized disease of the central nervous system (CNS), or disease localized to the skin, eyes, and mouth.[49] Vesicular rash occurs in only approximately 60% of infants with CNS or disseminated disease.[17,49,50]

## Diagnosis

The clinical diagnosis of HSV infection is based on the typical location and appearance of vesicles and ulcers. The virus is readily isolated in tissue culture within 1 to 3 days, especially when samples are from first episode infections or are obtained early after the appearance of recurrent lesions (especially when vesicles are present). Speed and sensitivity of diagnosis are maximized with the shell vial method, which combines centrifugation onto coverslips and staining with fluorescein-conjugated monoclonal antibodies after 24 hours to detect synthesis of early-appearing HSV proteins. Detection of HSV DNA by PCR is very sensitive and specific and is the gold-standard method for diagnosis of HSV infection.[51,52] DNA PCR may be especially useful when assessing skin lesions that are recurrent or are being evaluated long after their appearance. In these cases, the HSV DNA remains in the healing lesions and scabs, even though HSV can no longer be cultured. PCR of mucosal and cutaneous sites in neonatal HSV disease has not been evaluated systematically, and culture of those sites in this population remains the standard of care until such comparative studies are completed. Direct immunofluorescence for HSV antigen can be performed on cells scraped from skin, conjunctiva, or mucosal lesions.[53] The sensitivity of this method may be less than 75%, often because it is difficult to obtain evaluable specimens, but the results are usually available the same day.

The preferred diagnostic method for evaluation of children with suspected HSV meningoencephalitis is detection of HSV DNA in the cerebrospinal fluid (CSF), because cultures of CSF are usually negative. Sensitivity of HSV PCR is generally considered to be ≥95% for CSF samples, especially if the samples are obtained more than 3 days after onset of herpes encephalitis.[48,54] In one study of participants with brain biopsy-proven HSV encephalitis, the sensitivity of HSV PCR was 98%.[55] In a report of 15 patients being treated for proven HSV encephalitis, the CSF HSV PCR remained positive for a mean of 10 days after neurologic symptom onset.[56] In neonatal CNS HSV disease, CSF PCR has been reported to have a sensitivity of 75% to 100% and a specificity of 71% to 100%.[48,57] HSV PCR of blood may be used adjunctively in the diagnosis of HSV infection in neonates and other at-risk populations, but its sensitivity remains to be fully defined.[20,58] Definitive diagnosis of HSV esophagitis requires endoscopy with biopsy. Histologic evidence of HSV includes multinucleated giant cells with intranuclear viral inclusions, but diagnosis is established by staining the biopsy with HSV-specific monoclonal antibodies and/or culture or PCR of the tissue.

The rapid onset of poor vision, eye pain, and/or red eye (especially if red eye is associated with decreased vision or pain) should prompt a referral to an ophthalmologist, because these symptoms may be caused by herpesviruses or other pathogens that require specialized diagnostic testing (including fluorescein staining to detect characteristic dendritic corneal ulceration, advanced fundoscopic examination, and sampling of vitreous humor for PCR) and treatment approaches.

Typing of HSV isolates (or genotyping of amplicons) can provide prognostic information. For example, the frequency of recurrence after genital HSV-1 infection in patients without HIV is significantly less than after HSV-2 infection.[59,60]

## Prevention Recommendations

### *Preventing Exposure*

Exposure to HSV-1 is frequent in childhood. Although avoiding direct contact with secretions from adult caretakers, siblings, or other close contacts with active herpes labialis is intuitive, it is likely that most infections result from unrecognized exposure to the frequent asymptomatic shedding of HSV by individuals with prior infection.

Male condoms are effective in preventing many sexually transmitted diseases, including HIV.[61,62] When used consistently and correctly, male latex condoms reduce the risk of type 2 genital herpes.[63] An early study in participants in an HSV vaccine trial demonstrated some protection against HSV infection with condom use, which varied with gender and frequency of sexual activity.[64] A similar, but larger trial demonstrated a 26% reduction in HSV-2 genital infection, but not in HSV-1 infection, with condom use.[65] Protection was related to the proportion of sex acts that were protected with a condom. In a pooled analysis of 6 studies, condom use reduced the risk of HSV-2 acquisition by 30%, and the risk of HSV-2 acquisition increased steadily with each unprotected sex act.[63] A separate analysis of the pooled data estimated that the odds of HSV-2 acquisition with each sexual act were 3.6%, 2.7%, and 0% when condoms were never used, sometimes used, or always used, respectively.[66]

Individuals with HIV should use latex condoms consistently and correctly during sexual intercourse to protect sexual partners and reduce (not eliminate) the risk of acquiring HSV and other sexually transmitted pathogens. They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident. However, most genital herpes infections are transmitted by genital-genital or oral-genital contact from asymptomatic shedding of HSV when their partners are not experiencing a clinical recurrence or are unaware that they are infected. Condoms will not protect against orogenital transmission and infection transmitted prior to penetration.

Administration of chronic suppressive therapy to individuals with HIV and HSV to reduce clinical recurrences also reduces HSV-2 transmission to susceptible HSV-discordant partners without HIV by 25% to 75% and can reduce HSV shedding in patients with HIV/HSV co-infection.[67-71] Although these reductions in transmission and shedding are less than reductions in clinical disease observed with suppressive therapy, when administered to prevent clinical recurrences, suppressive therapy may thus limit spread to sexual partners. All HSV-active antivirals are equally effective in reducing transmission, but twice-daily dosing may be superior to a larger once-daily dose.[69] ART also reduces the frequency of asymptomatic HSV shedding.[15]

Transmission of HSV to fetuses and neonates born to pregnant women with HSV/HIV coinfection can occur, but the likelihood is low. Effective ART regimens may decrease, but not prevent, maternal genital HSV shedding and recurrence of genital lesions.[15] Use of acyclovir or valacyclovir near term suppresses genital HSV outbreaks and shedding in late pregnancy in women with recurrent genital herpes who do not have HIV and reduces the need for cesarean delivery for recurrent HSV.[72] Although the study demonstrating these results had insufficient sample size to determine the effect of prophylaxis on neonatal infection, the American Congress of Obstetricians and Gynecologists (ACOG) recommends that pregnant women with recurrent genital herpes who do not have HIV be offered suppressive antiviral therapy at or beyond 36 weeks of gestation.[73] The safety and efficacy of this strategy have not been evaluated in women with HIV/HSV-2 coinfection, who may have less HSV-2-specific antibody and/or T-cell function and are more likely to have both symptomatic and asymptomatic reactivation of genital HSV. Currently, there is not sufficient data in this population on which to base a specific recommendation regarding this strategy. Importantly, neonatal HSV disease can occur following delivery among women on suppressive antiviral therapy,[74] illustrating that protective effects of maternal suppression are not absolute. Elective cesarean delivery, preferably before rupture of membranes, is recommended for all women, both those with and without HIV, who have active genital HSV lesions at the onset of labor.[75-77]

### *Preventing Disease*

Antiviral prophylaxis before or after potential sexual exposure to HSV has been used successfully to prevent HSV acquisition but has not been studied in patients with HIV and **is not recommended**.[78]

## Treatment Recommendations

### *Treating Disease*

Acyclovir is the drug of choice for treatment of local and disseminated HSV in infants and children, regardless of HIV-infection status. Neonatal HSV disease should be treated with intravenous (IV) acyclovir (20 mg/kg body weight three times a day) administered for at least 21 days for CNS and disseminated disease and for 14 days for disease localized to the skin, eyes, and mouth.[79] IV acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay at or after 21 days of treatment is negative.

Treatment of HSV encephalitis or disseminated HSV is the same for children and adolescents with and without HIV. IV acyclovir is the drug of choice. Beyond the neonatal period, HSV encephalitis should be treated for 21 days (10–15 mg/kg body weight three times a day, with dose determined by age and body size).[47,48]

Children and adolescents with severe mucocutaneous HSV lesions or organ involvement (e.g., esophagitis) should receive IV acyclovir (5–10 mg/kg per dose every 8 hours).[80-82] Patients with severe mucocutaneous lesions can be changed to oral antiviral therapy after their lesions have begun to regress. Duration of therapy will depend on the rate and character of healing, but therapy should be continued until all lesions have completely healed. Failure to heal, or a marked delay or change in rate of healing, should raise concern for acyclovir resistance.[83,84]

Oral acyclovir, valacyclovir, or famciclovir are used to treat genital HSV episodes, generally for periods of 5 to 14 days. First-episode genital (or orolabial) lesions in HIV-infected children or adolescents can be treated with oral acyclovir for 7 to 10 days as indicated by the response to therapy.[82,85,86] Patients with recurrent mucocutaneous lesions, if treated, generally receive oral acyclovir for 5 days.

Sufficient information exists to support the use of valacyclovir in children, especially given its 2- to 3-fold improved bioavailability as compared to acyclovir, at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day.[87] Lower doses may be insufficient for children weighing less than 20 kg.[88-90] No pediatric formulation is available and valacyclovir can generally only be used for children old enough to swallow the large tablets, although crushed valacyclovir tablets can be used to make an extemporaneous suspension with reliable bioavailability and shelf life following instructions that are included in the U.S. Food and Drug Administration (FDA) Package Insert.[89,91] A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation or who are too small for available pills. A schedule for weight-adjusted dosing is available to inform dosing of small children.[92] Because of their improved bioavailability, valacyclovir and famciclovir administered at higher doses for only 1 to 3 days often is sufficient to manage recurrent genital HSV infection in HIV-uninfected adults, and these regimens have been used safely in HIV-uninfected children.[93,94] However, these short regimens have not been recommended for HIV-infected adolescents and adults.[82]

Treatment for acute retinal disease caused by HSV should be guided by an ophthalmologist. HIV-infected patients with acute retinal necrosis should be on ART and receive IV acyclovir (10–15 mg/kg body weight IV every 8 hours for 10–14 days), followed by prolonged (i.e., 4–6 weeks) oral therapy, such as with valacyclovir or acyclovir.[95] HSV keratoconjunctivitis is usually treated with topical trifluridine or ganciclovir, although many experts recommend adding oral therapy.[96] Because of potential corneal toxicity of topical therapy, close follow-up by an ophthalmologist is recommended and duration of therapy should be individualized.

## *Monitoring and Adverse Events*

Primary toxicities of acyclovir are phlebitis (when administered IV), renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir and famciclovir, except for phlebitis. In infants receiving high-dose acyclovir for neonatal disease, neutropenia (defined as absolute neutrophil count <1,000/mm$^3$) occurs in approximately 20% of treated neonates.[79] Among severely ill children who were HIV-uninfected and received high-dose IV acyclovir, renal injury or failure was observed in >10% of patients.[97] It is recommended that renal function be determined at initiation of IV acyclovir treatment and at least once weekly for the duration of treatment, particularly in those who have underlying renal dysfunction and are receiving prolonged therapy. If possible, avoid other nephrotoxic drugs. IV acyclovir must be diluted adequately and administered slowly over 1 to 2 hours. Since acyclovir is excreted primarily by the kidney, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure.

## *Managing Treatment Failure*

Resistance of HSV to acyclovir occurs in 5% to 10% of immunocompromised patients.[98] This results from the mutation frequency of HSV, the virostatic nature of acyclovir, and the inadequacy of HSV-specific cell-mediated immunity to rapidly clear the HSV infection. Resistance to antiviral drugs should be suspected if systemic involvement and skin lesions do not begin to resolve within 5 to 7 days after initiation of therapy, skin lesions are atypical in appearance, or satellite lesions appear after 3 to 4 days of therapy. If possible, a lesion culture should be obtained and if virus is isolated, susceptibility testing performed to confirm resistance. This may be difficult to arrange, and results may not be readily available. Thus, the decision to change therapy is often based on clinical observations. All acyclovir-resistant HSV strains are resistant to valacyclovir, and it is very rare that they are sensitive to famciclovir. The therapeutic choice for acyclovir-resistant herpes is foscarnet.[82,83,99,100] Foscarnet has significant nephrotoxic potential; up to 30% of patients experience increases in serum creatinine levels. It also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. For patients receiving foscarnet, complete blood count, serum electrolytes, and renal function should be monitored twice weekly during induction therapy and once weekly thereafter. Infusing foscarnet after saline fluid loading can minimize renal toxicity. Doses should be modified in patients with renal insufficiency.

IV cidofovir is recommended for patients with HSV resistant to acyclovir and foscarnet.[82,83] For disease limited to a small number of indolent, non-healing lesions, topical formulations of trifluridine, foscarnet, and cidofovir have been used successfully, although this will require local preparation of the topical formulations and may require prolonged application for 21 to 28 days or longer.[101]

## *Preventing Recurrence*

Administration of oral acyclovir prophylaxis (suppressive therapy) for 6 months can prevent cutaneous recurrences of HSV after neonatal disease of the CNS or skin, eyes, and mouth in infants without HIV and is associated with better neurodevelopmental outcome in those with CNS disease.[102]

Because recurrent episodes of mucocutaneous HSV disease can be treated successfully, chronic prophylaxis with acyclovir or other available antivirals against HSV is not required for patients who develop HSV infection beyond the neonatal period. Effective ART may decrease recurrences. Children who have frequent, severe, or troubling recurrences (i.e., 4 to 6 severe episodes a year) can be given daily prophylaxis with oral acyclovir; daily valacyclovir or famciclovir also are options for prophylaxis in adolescents.[69,82] Prophylaxis may be desired not only because recurrences may be especially problematic in patients with severe immune suppression, but also for cosmetic or psychosocial reasons. Use of suppressive antiviral drugs against HSV in adults reduces recurrences by 30% to 60%, and in adults with HIV receiving ART, symptomatic recurrences are reduced by 60% to 75%.[67,68,103]

Because corneal clouding can occur due to the stromal reaction of recurrent keratoconjunctivitis, many ophthalmologists use acyclovir prophylaxis to reduce the frequency of ocular recurrences. However, resistance to acyclovir has been reported in this circumstance in patients without HIV.[104]

### *Discontinuing Secondary Prophylaxis*

Patients receiving prophylactic therapy should be evaluated annually for the need to continue prophylaxis. Cessation of secondary prophylaxis will be determined by the level of immune reconstitution, frequency and severity of recurrences, individual tolerance of recurrent episodes, and location of recurrence (e.g., recurrent keratitis may require longer prophylaxis because of risk of vision-impairing disease).

## Recommendations

### *Primary Prevention*

**I. Will using condoms, compared to not using condoms, prevent HSV infection in sexually active adolescents and young adults with HIV?**

- Condoms should be used to prevent HSV (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.
- Male condoms are effective in preventing many sexually transmitted diseases, including HIV. A large observational trial on condom use and HSV acquisition demonstrated a 26% reduction in HSV-2 genital infection, but not in HSV-1 infection.[65] A pooled analysis of 6 similar studies concluded that condom usage resulted in a 30% lower risk of HSV-2 acquisition as compared to no condom use.[63,66] Patients with HIV should use latex condoms consistently and correctly during sexual intercourse to reduce the risk of acquiring HSV and other sexually transmitted pathogens and to protect sexual partners.

### *Secondary Prevention*

**II. Will adolescents and young adults with HIV who have recurrent genital HSV infection benefit from suppressive anti-HSV antiviral therapy as compared to 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)**.
- Placebo-controlled trials demonstrated that antiviral drugs against HSV, administered for recurrent HSV disease in adults with HIV who are receiving ART, reduced symptomatic recurrences by 60% to 75%. This is an option for patients with frequent, severe, or troubling HSV recurrences. Chronic suppressive therapy in individuals with HSV also reduced HSV-2 transmission to susceptible partners without HIV by 25% to 75%.[67-69]

### *Treatment*

**III. Should children and adolescents with HIV with severe primary or recurrent HSV (genital or orolabial) infection receive IV acyclovir as compared to not receiving IV 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)**.

- Placebo-controlled trials in children and youth with immunocompromising conditions (other than HIV infection) indicate that those with severe mucocutaneous HSV lesions or organ involvement benefitted from IV acyclovir.[80,81] Patients with severe mucocutaneous lesions can be switched to oral antiviral therapy after their lesions have begun to regress. Duration of therapy will depend on the rate and character of healing, but therapy should be continued until lesions have completely healed. Failure to heal, or a marked delay or change in rate of healing, should raise concern for acyclovir resistance.

**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. Valacyclovir and famciclovir have superior pharmacokinetics **(strong; moderate)**.
- Controlled trials in children without HIV and adults with HIV indicate that treatment of first-episode orolabial or genital HSV lesions results in reduction in duration and severity of lesions.[85,86] Recurrent mucocutaneous lesions also benefit from treatment. Because of their improved bioavailability, valacyclovir and famciclovir can be administered less frequently and will achieve higher serum antiviral levels when compared with acyclovir. Both alternatives have been safely used in children without HIV.[92,93]

**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.

  Resistance of HSV to acyclovir occurs in 5% to 10% of immunocompromised patients. Resistance to antiviral drugs should be suspected if systemic involvement and skin lesions do not begin to resolve within 5 to 7 days after initiation of therapy. The decision to change therapy often is based on clinical observations because virus isolation and testing for resistance take many days. The therapeutic choice for acyclovir-resistant herpes is foscarnet, based primarily on the sensitivity pattern of HSV isolates from HSV infections unresponsive to acyclovir in immunocompromised patients[99,100] and expert opinion. Patients receiving foscarnet should have electrolytes and renal function monitored twice weekly during induction therapy and once weekly thereafter. The package insert contains an algorithm for drug infusion and dose modification for patients with renal insufficiency.

## Dosing Recommendations for Prevention and Treatment of Herpes Simplex Virus Infections (page 1 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Prophylaxis | None | None | Primary prophylaxis is not indicated. |
| Secondary Prophylaxis | <u>Mucocutaneous Disease</u>:<br>• Acyclovir 20 mg/kg body weight/ dose (maximum 800 mg/dose) by mouth BID<br><u>Suppressive Therapy After Neonatal HSV Disease (Skin, Eye, Mouth, CNS, or Disseminated Disease)</u>:<br>• Acyclovir 300 mg/m$^2$ body surface area/dose by mouth TID for 6 months | <u>Mucocutaneous Disease, for Adolescents Old Enough to Receive Adult Dosing</u>:<br>• Valacyclovir 500 mg by mouth BID, or<br>• Famciclovir 500 mg by mouth BID | <u>Secondary Prophylaxis Indicated</u>:<br>• Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease.<br><u>Criteria for Discontinuing Secondary Prophylaxis</u>:<br>• After a prolonged period (e.g., 1 year) of prophylaxis, consider suspending prophylaxis and determine with the patient whether additional prophylaxis is necessary. Although level of immune reconstitution is a consideration, no specific CD4 threshold has been established. |
| Treatment | <u>Neonatal CNS or Disseminated Disease</u>:<br>• Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for ≥21 days<br><u>Neonatal Skin, Eye, or Mouth Disease</u>:<br>• Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for 14 days<br><u>CNS or Disseminated Disease in Children Outside the Neonatal Period</u>:<br>• Acyclovir 10 mg/kg body weight (up to 15 mg/kg body weight/dose in children <12 years) IV every 8 hours for 21 days<br><u>Moderate to Severe Symptomatic Gingivostomatitis</u>:<br>• Acyclovir 5–10 mg/kg body weight/ dose IV every 8 hours. Patients can be switched to oral therapy after lesions have begun to regress and therapy continued until lesions have completely healed.<br><u>Mild Symptomatic Gingivostomatitis</u>:<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 7–10 days<br><u>Recurrent Herpes Labialis</u>:<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 5 days<br><u>For First-Episode Genital Herpes (Adults and Adolescents)</u>:<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 7–10 days | • Valacyclovir is approved for immunocompetent adults and adolescents with first-episode mucocutaneous HSV at a dose of 1 g by mouth BID for 7–10 days; also approved for recurrent herpes labialis in children ≥12 years using two, 2-g doses by mouth separated by 12 hours as single-day therapy.<br>• Recurrent genital HSV can be treated with valacyclovir 500 mg BID for 3 days or 1 g by mouth daily for 5 days.<br>• Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth BID for 1 day.<br>• Famciclovir is approved to treat primary genital HSV in immunocompetent adults at a dose of 250 mg/dose by mouth TID for 7–10 days.<br>• Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth BID at a 12-hour interval for 2 doses.<br>• Famciclovir is approved for use in HIV-infected adults and adolescents with recurrent mucocutaneous HSV infection at a dose of 500 mg/dose by mouth BID for 7 days.<br><u>Acyclovir-Resistant HSV Infection</u>:<br>• Foscarnet 40 mg/kg body weight/ dose given IV every 8 hours (or 60 mg/kg body weight/dose IV every 12 hours) should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/ minute). | <u>For Neonatal CNS Disease</u>:<br>• Repeat CSF HSV DNA PCR should be performed on days 19 to 21 of therapy. If the repeat CSF HSV DNA PCR is positive, continue IV acyclovir for an additional week, repeating the CSF HSV DNA PCR again near the end of extended treatment. Acyclovir should not be stopped until a repeat CSF HSV DNA PCR is negative.<br>• There is no pediatric preparation of valacyclovir (although crushed capsules can be used to make a suspension according to specific instructions provided in the U.S. FDA package insert) and data on dosing in children are limited. Valacyclovir can be used by adolescents able to receive adult dosing.<br>• Famciclovir is available in a sprinkle formulation with weight-adjusted dosing. Famciclovir can be used by adolescents able to receive adult dosing.<br><u>Alternative and Short-Course Therapy in Immunocompromised Adults with Recurrent Genital Herpes</u>:<br>• Acyclovir 800 mg per dose by mouth BID for 5 days<br>• Acyclovir 800 mg per dose by mouth TID for 2 days<br><u>Note</u>: Consultation with an ophthalmologist experienced in managing herpes simplex infection involving the eye and its complications in children is strongly recommended when ocular disease is present. |

**Dosing Recommendations for Prevention and Treatment of Herpes Simplex Virus Infections** (page 2 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment, continued | <u>Recurrent Genital Herpes (Adults and Adolescents)</u>:<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 5 days<br><u>Children with HSV Keratoconjunctivitis</u>:<br>• Often treated with topical trifluridine (1%) or ganciclovir (0.15%) applied as 1–2 drops 5 times daily. Many experts add oral acyclovir to the topical therapy.<br><u>Children with ARN</u>:<br>• For children old enough to receive adult dose, acyclovir 10–15 mg/kg body weight/dose IV every 8 hours for 10–14 days, followed by oral valacyclovir 1 g/dose TID for 4–6 weeks<br>• As an alternative, oral acyclovir 20 mg/kg body weight/dose QID for 4–6 weeks after IV acyclovir for 10–14 days | | |

Key to Acronyms: ARN = acute retinal necrosis; BID = twice a day; CD4 = CD4 T lymphocyte; CNS = central nervous system; FDA = Food and Drug Administration; CSF = cerebrospinal fluid; HSV = herpes simplex virus; IV = intravenous; PCR = polymerase chain reaction; QID = four times a day; TID = three times a day

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# 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/mm$^3$ 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/mm$^3$ 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*

## Epidemiology

Histoplasmosis is caused by inhalation of microconidia produced by the mycelial form of *Histoplasma capsulatum*, an endemic dimorphic fungus, and cases have been reported from all continents except Antarctica. In the United States, it is most highly endemic in the Ohio and Mississippi river valleys. Infections in regions in which histoplasmosis is not endemic often result from travel to endemic regions within and outside the United States (e.g., Mexico, Central and South America). Risk factors predisposing to infection are exposure to activities that disturb contaminated sites and are accompanied by aerosolization of spores and (in HIV-infected adults) a CD4 T lymphocyte (CD4) cell count <150 cells/mm$^3$. Because yeast forms of the fungus may remain viable within granulomas formed after successful treatment or spontaneous resolution of infection, late relapse can occur if cellular immune function wanes, although the magnitude of this risk appears very low.[1] Infection can occur during pregnancy, and transplacental infection has rarely been reported.[2]

During the era before combination antiretroviral therapy (cART), histoplasmosis was reported in 2% to 5% of HIV-infected adults living in regions with endemic disease; rates of 25% have been reported in some cities.[3] In a highly endemic region, histoplasmosis was the AIDS-defining illness in 25% of adults and 8% of children.[4] Progressive disseminated histoplasmosis (PDH) occurred in 5% of HIV-infected children in another highly endemic region (M. Kleiman, unpublished data). The overall incidence of histoplasmosis in children has not been examined systematically but appeared to be low, even during the pre-cART era.[5] An HIV-positive infant with probable congenital histoplasmosis has been reported in a non-endemic area.[6]

Few epidemiologic data have been reported on disseminated histoplasmosis in HIV-infected children and adolescents treated with cART. In several combined Pediatric AIDS Clinical Trial Group cohorts, the incidence rate of all non-*Candida* invasive fungal infection was 0.10 infections per 100 child-years (95% CI 0.05–0.20) during the pre-cART era, and 0.08 infections per 100 child-years (95% CI 0.03–0.17) since the advent of cART.[5,7] These data were contributed from centers that underrepresented the geographic regions of maximal histoplasmosis prevalence, so the statistical power to detect decreases in incidence rates associated with cART may have been limited. However, none of the rates of domestic endemic fungal infections (e.g., histoplasmosis, coccidioidomycosis, and blastomycosis) are likely to exceed these estimates in HIV-infected children and adolescents.

## Clinical Manifestations

In HIV-uninfected children, acute pulmonary manifestations are common; chronic pulmonary infection has not been described. Because of greater airway pliability in children, airway obstruction from mediastinal lymphadenopathy is more common in children.[8] Meningitis often accompanies progressive disseminated infection in infancy; subacute meningitis and parenchymal lesions characteristic of central nervous system (CNS) disease in adults are unusual in children.[9] Isolated pulmonary granulomas resulting from past infections are common incidental findings in chest radiographs of asymptomatic persons who have resided in histoplasmosis-endemic regions.

The most frequent clinical manifestation of histoplasmosis in HIV-infected children with AIDS is PDH, which is fatal if untreated. Prolonged fever and failure to thrive are uniform presenting complaints. Few reports have been published of presenting signs and symptoms in children with PDH complicating AIDS.[4,10-12] However, most are similar to those seen in PDH in otherwise normal infants and in infections in patients with other primary or acquired cellular immunodeficiencies. These include splenomegaly, cough, respiratory distress, hepatomegaly, septic appearance, generalized lymphadenopathy, interstitial pneumonitis, cytopenia(s), coagulopathy, oropharyngeal/gastrointestinal (GI) ulcerations, and erythematous nodular/ulcerative cutaneous lesions.[13-15]

## Diagnosis

Culture and histopathologic, serologic, antigen-detection, and molecular diagnostic techniques have been developed to aid in diagnosing histoplasmosis.[16,17] Understanding their uses and limitations is essential to interpreting results.

Histoplasmin skin tests are no longer available and were not useful in diagnosing disseminated disease.[14,15] Although isolation of the fungus using culture is diagnostic, it often requires invasive procedures, is insensitive, and may take 10 to 30 days for growth to occur. Lysis-centrifugation methodology facilitates growth of *H. capsulatum*, and a DNA probe permits prompt identification of isolates.[18] Histopathologic demonstration of typical yeast forms in tissue specimens, bone marrow, or peripheral blood can be performed rapidly and, when positive, is highly suggestive of active infection. However, results are positive in only 12% to 43% of adults with PDH.[16] Polymerase chain reaction and DNA probes have been developed to detect *H. capsulatum* DNA in tissues[19] and body fluids[20] but neither is sufficiently sensitive and DNA probes may lack adequate specificity.[16,17]

Interpretation of serologic testing using complement fixation (CF) and immunodiffusion methods is problematic in immunocompromised hosts with PDH. CF titers of ≥1:32 to the yeast and/or mycelial antigens or detection of H and/or M bands with the immunodiffusion test are considered strongly suggestive of active or recent infection. However, only 41% to 69% of HIV-infected adults are seropositive, compared with 82% of adults with PDH and no underlying immunodeficiency.[21,22] Thus, seronegativity cannot be used to exclude active infection, especially PDH. Although a fourfold increase in CF antibody is diagnostic of active infection, 2 to 4 weeks is needed to determine this. CF antibody titers of cerebrospinal fluid (CSF) may be useful for diagnosing meningitis. In these instances, the assay should begin with undiluted specimens. Concurrent serum titers should be evaluated to exclude false positivity caused by blood contamination of the CSF.[9]

An enzyme-linked immunoassay (EIA) that rapidly identifies and quantifies histoplasma antigen in body fluids fills most of the gaps left by other diagnostic methods.[22] EIA is especially suited for evaluating patients with large fungal burdens, a feature of infection in immunocompromised hosts. EIA can detect antigen in serum, bronchoalveolar lavage, and CSF specimens. The reported sensitivity of antigen detection is 91% to 92% in adults with PDH, and 95% in adults with AIDS;[16,17] sensitivity in children with underlying cellular immunodeficiency, including those who are HIV-infected, and in otherwise normal infants approaches 100%.[14,23]

The third-generation EIA is standardized by extrapolating antigen concentrations from a calibration curve that is linear to a value of 39 ng/mL. However, urine antigen concentrations in serious infections frequently exceed this value. In these instances, serum specimens should be followed because maximum serum concentrations are lower than those in urine and thus more likely to be in a range in which differences can be accurately measured. After resolution of the antigenemia, urine concentrations can be followed to monitor the effectiveness of treatment and, thereafter, to identify relapse. Antigenuria is identified in 90% of patients whose histoplasmosis relapses.[8] Interpretation is complicated by cross-reactions with blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infections.[16,17] Distinctive clinical and geographic features of these endemic fungal infections permit accurate differentiation. Urine antigen is detectable in 75% to 81% of immunocompetent hosts with acute, primary pulmonary infection. This occurs early in infection, reflecting the primary fungemia that is aborted by an effective cellular immune response. Thus, antigenuria in a patient with HIV who retains normal cellular immunity may not necessarily presage development of disseminated infection. Based on adult data, testing both serum and urine following high inoculum exposure may improve sensitivity of detecting antigen in acute primary pulmonary infection, especially in patients with less severe CD4 depletion and milder illness, in whom sensitivity in urine may be lower.[24]

Diagnosis of CNS infection is difficult, particularly in patients who have isolated meningitis without disseminated disease.[9] Highest sensitivity is achieved by testing CSF for histoplasma antigen, antibody, and large-volume culture. In adults, CSF culture is positive in 20% to 60% of patients, CSF antigen is positive in 40% to 70%, and CSF antibody is positive in 70% to 90%.[16,17] Meningitis frequently accompanies PDH of infancy,[13] an entity that has not been associated with a recognized immunodeficiency disorder.

## Prevention Recommendations

### *Preventing Exposure*

Most infections occur without a recognized history of exposure to a high-risk site or activity. Therefore, complete avoidance of exposure in histoplasmosis-endemic regions is not possible. Sites and conditions sometimes implicated in high-risk exposure and point-source outbreaks include disturbances of contaminated areas resulting in aerosolization of spores. These include soil contaminated with bird or bat droppings, older urban and rural structures, decaying vegetation or trees, and caves. Dry and windy conditions, excavation, demolition, renovation, gardening, and agricultural activities often predispose to aerosolization of spores. Education should be directed toward avoidance of these activities. If not feasible, reducing the release of spores by wetting soil, renovation sites, and other potentially contaminated areas, and use of protective respiratory devices,[25] should be recommended.

### *Preventing First Episode of Disease*

Prophylaxis with itraconazole is recommended for HIV-infected adults with CD4 counts <150 cells/mm$^3$ and who reside in areas where histoplasmosis is highly endemic (that is, incidence >10 cases per 100 patient-years) and in instances in which risk of occupational exposure is high. Prophylaxis has no effect on survival.[8] Given the low incidence of histoplasmosis in HIV-infected children, possibility for drug interaction, development of antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of histoplasma infections in children is not recommended **(BIII)**.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

PDH is fatal without treatment. The clinical response to amphotericin B is faster than that of itraconazole and it is preferred for initial treatment of severe infections **(AI*)**. Following amphotericin B induction, itraconazole, the azole preferred for treatment of histoplasmosis **(AI*)**,[8] is used to complete the course of therapy. A trial in adults[26] demonstrated that induction with liposomal amphotericin B was associated with less toxicity and improved survival, compared with induction using amphotericin B deoxycholate. Recommendations for HIV-infected children are derived from trials in adults and from anecdotal experience in children.[8] Because of important differences in managing PDH in children, consultation with experts should be considered.

Itraconazole is usually well tolerated in children. Itraconazole has a long half-life and reaches steady-state levels at 2 weeks. The interval needed to achieve desired serum concentrations can be shortened if the recommended dose is administered 3 times daily for the first 3 days of therapy (i.e., loading dose); the recommended dose, administered twice daily, should be started thereafter. **<u>Itraconazole solution is preferred to the capsule formulation because it is better absorbed and serum concentrations are 30% higher than those achieved with the capsules</u>.** The solution should be taken on an empty stomach or with a carbonated beverage. If capsules are used, they should be taken with meals. Because absorption of itraconazole varies considerably from patient to patient, serum concentrations should be measured to ensure effective levels of drug, monitor changes in dosage, and assess compliance **(BIII)**. The minimal inhibitory concentration of *H. capsulatum* is 0.01 µg/mL, and although minimally effective serum concentrations have not been determined, a serum concentration of 1.0 µg/mL is recommended; dosage should be reduced if concentrations exceed 10 µg/mL.[8]

Fluconazole is an alternative for patients with mild histoplasmosis and who are intolerant of itraconazole or in whom desired serum levels of itraconazole cannot be attained. Fluconazole is less effective than itraconazole and has been associated with development of drug resistance.[27]

#### Acute Primary Pulmonary Histoplasmosis

Patients with acute primary pulmonary histoplasmosis can present with a wide spectrum of symptoms, ranging from dyspnea with high fever to only mild respiratory symptoms, and variable fever. Chest radiographs may show mediastinal adenopathy with or without focal pulmonary infiltrate and/or a diffuse miliary-like pattern in high-inoculum exposure; radiographic findings may mimic those of tuberculosis. For severe or moderately severe symptoms, liposomal amphotericin B should be administered for 1 to 2 weeks **(AI*)**.[8] After clinical improvement, adults with CD4 counts >300 cells/mm$^3$ and, by extrapolation, HIV-infected children with CD4 percentage >20% or, if ≥ 6 years, CD4 count >300 cells/mm$^3$, should receive itraconazole, beginning with a loading dose (see above) for the first 3 days, followed by the recommended doses administered twice daily for at least 12 weeks **(AIII)**. All other HIV-infected children should receive itraconazole for 12 months **(AIII)**. Urine antigen usually is elevated in these situations and should be monitored to gauge clinical response and, after treatment, identify relapse **(AIII)**.

HIV-infected children, particularly those with CD4 percentage >20% (or, if ≥ 6 years, CD4 counts >300 cells/mm$^3$) compatible with functional cellular immunity, occasionally present with fever, mild primary pulmonary infection, and histoplasma antigenuria. Although an effective cellular immune response may limit such illnesses, it may be prudent to treat with itraconazole for 12 weeks and monitor histoplasma urine antigen concentrations to ensure that concentrations decrease **(BIII)**.

### Moderately Severe to Severe PDH

Data derived from experience in HIV-infected adults suggest that HIV-infected children with moderately severe to severe disseminated histoplasmosis should be treated with an IV amphotericin B formulation for ≥2 weeks (and until they clinically improve), followed by itraconazole for 12 months **(AI*)**. HIV-infected adults with moderately severe to severe PDH have a higher response rate to treatment with liposomal amphotericin B than with the deoxycholate formulation (88% vs. 64%) and a lower death rate (2% vs. 13%); therefore liposomal preparations are preferred in adults and, by extrapolation, in children **(AI*)**.[8] A loading dose (see above) of itraconazole should be used for the initial 3 days. If itraconazole is not well tolerated, a 4- to 6-week course of amphotericin B can be used **(AIII)**. Progressive decline in histoplasma urine and serum antigen levels is expected with effective treatment, and monitoring levels for lack of such decline can detect relapse.

Although therapeutic trials of amphotericin B deoxycholate used to treat PDH in HIV-infected children have not been performed, this formulation is effective for treating severe PDH in infants,[13,28] including those with CNS infection,[13] and in children with other primary or acquired immunodeficiency states. Amphotericin B deoxycholate is better tolerated by children than by adults, and it is less costly than other formulations. It can be used if cost or availability of lipid formulations precludes their use **(AIII)**.

### Mild to Moderate PDH

In 80% to 100% of patients without signs of CNS infection, mild to moderate PDH responds favorably to itraconazole monotherapy for 12 months **(AII*)**.[8,29] This regimen also is recommended for HIV-infected children with mild to moderate PDH **(AII*)**. A loading dose of itraconazole (see above) should be administered at the onset of treatment and serum concentrations monitored. Urine antigen concentrations should also be monitored.

### CNS Infection

CNS infection that accompanies PDH is expected to respond to the regimen recommended for moderately severe to severe PDH. Isolated CNS infection is unusual in children. In adults, frequent failure and relapse are common, and aggressive therapy is recommended. Penetration into the CSF is poor with all amphotericin B formulations. Liposomal amphotericin B is preferred for CNS disease in children and adults because it achieves higher concentrations in the brain **(AII*)**; the deoxycholate formulation is an alternative. Another lipid formulation can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B **(AIII)**. Amphotericin should be administered for 4 to 6 weeks. Thereafter, a child should receive a loading dose of itraconazole and continuation of itraconazole for 12 months and until CSF abnormalities, including histoplasma antigen, have resolved **(AII*)**.

Itraconazole levels should be followed and the dose adjusted to ensure optimal serum concentrations **(AIII)**.

### Asymptomatic Histoplasma Granuloma

In asymptomatic HIV-infected children who have intact cellular immunity (meaning CD4 >15% for all ages and CD4 cell count >150 cells/mm$^3$ for ages ≥6 years) and have resided in an area with endemic histoplasmosis, the presence of a typical granuloma in a chest radiograph should prompt evaluation of histoplasma urine antigen and both CF and immunodiffusion antibody. If any of these tests are positive, treatment with itraconazole for 12 weeks is prudent **(BIII)**. If these tests are negative, therapy need not be used, and close clinical follow-up is recommended. In either instance, histoplasma urine antigen testing should be considered if unexplained fever, weight loss, or other systemic symptoms occur.

### Monitoring and Adverse Events (Including IRIS)

In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for a year thereafter to identify relapse **(AIII)**.[8] After a recommended course of therapy and in the absence of symptoms, low-level, stable antigenuria may not constitute a basis for prolonging the recommended course of therapy. Serum levels of itraconazole should be monitored in patients receiving treatment **(AIII)**.

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

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

Immune reconstitution inflammatory syndrome (IRIS) caused by an inflammatory response to histoplasmosis unmasked by cART-induced improvement in cellular immunity is unusual, and symptoms are often mild.[30] In the event of IRIS, cART should be continued along with antifungal therapy **(AIII)**. IRIS related to histoplasmosis has not been reported in children.

### Managing Treatment Failure

Both voriconazole and posaconazole have been used successfully in a small number of refractory cases in adults.[8] Because little experience has been reported using the newer azoles and data are limited on use of these agents in children, expert consultation is recommended for cases refractory to first-line agents.

### Preventing Recurrence

Following initial amphotericin B treatment (induction) and subsequent oral itraconazole consolidation therapy for at least 1 year, longer-term suppressive therapy with itraconazole may be required in HIV-infected children who remain immunosuppressed (i.e., CD4 percentage <15% at any age or <150 cells/mm$^3$ in children aged ≥6 years) and in those who experience relapse despite receipt of appropriate therapy **(AII*)**.[8,31] Fluconazole is less effective than itraconazole **(CII*)**, and experience with voriconazole is limited in children. Adherence to both antifungal treatment and cART should be monitored carefully, as non-adherence can increase the risk of relapse.

### Discontinuing Secondary Prophylaxis

Discontinuation of secondary prophylaxis (suppressive therapy) has not been examined in children. Based on data from a clinical trial, adults with immune restoration on cART can discontinue itraconazole if itraconazole has been received for ≥1 year, blood cultures are negative, histoplasma serum antigen is <2 ng/mL, CD4 counts are >150 cells/mm$^3$, and there is good adherence to cART.[31] Extrapolating these recommendations to HIV-infected children on cART with immune restoration (meaning CD4 percentage ≥15% at any age; CD4 count >150 cells/mm$^3$ in children aged ≥6 years) seems reasonable **(CIII)**. Secondary prophylaxis should resume if these parameters are not met. Chronic suppressive therapy is recommended for relapse that occurs despite appropriate treatment **(BIII)**.

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**Dosing Recommendations for Preventing and Treating Histoplasmosis** (page 1 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis** | N/A | N/A | Primary Prophylaxis indicated for selected HIV-infected adults but not children.<br><br>Criteria for Discontinuing Primary Prophylaxis:<br>• N/A<br><br>Criteria for Restarting Primary Prophylaxis:<br>• N/A |
| **Secondary Prophylaxis (Suppressive Therapy)** | Itraconazole oral solution 5–10 mg/kg body weight (maximum 200 mg) per dose by mouth daily | Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily | Secondary Prophylaxis Indicated:<br>• Documented histoplasmosis in a patient with impaired immune function<br><br>Criteria For Discontinuing Secondary Prophylaxis<br>*If All of the Following Criteria Are Fulfilled:*<br>• CD4 percentage >15% at any age; or CD4 cell count >150 cells/mm$^3$ aged ≥6 years.<br>• Received ≥1 year itraconazole maintenance therapy<br>• Established (e.g., ≥6 months) adherence to effective cART<br>• Negative *Histoplasma* blood cultures<br>• Serum Histoplasma antigen <2 ng/mL<br><br>Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules. |
| **Treatment** | Acute Primary Pulmonary Histoplasmosis:<br>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth twice daily for 12 months. Duration of 12 weeks is sufficient for HIV-infected children, with functional cellular immunity (CD4 percentage >20% or if aged ≥6, CD4 cell count >300 cells/mm$^3$), provided monitoring confirms clinical improvement and decreased urine antigen concentrations.<br><br>Mild Disseminated Disease:<br>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for | Acute Primary Pulmonary Histoplasmosis:<br>• Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily<br><br>Mild Disseminated Disease:<br>• Fluconazole 5–6 mg/kg body weight IV or by mouth (maximum 300 | Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules.<br><br>Urine antigen concentration should be assessed at diagnosis. If >39 ng/mL, serum concentrations should be followed. When serum levels become undetectable, urine concentrations should be monitored monthly during treatment and followed thereafter to identify relapse.<br><br>Serum concentrations of itraconazole should be monitored and achieve a level of 1 µg/mL at steady-state. Levels |

**Dosing Recommendations for Preventing and Treating Histoplasmosis** (page 2 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Treatment**, continued | first 3 days of therapy, followed by 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth twice daily for 12 months<br><br>Moderately Severe to Severe Disseminated Disease<br>*Acute Therapy (Minimum 2-Week Induction, Longer if Clinical Improvement is Delayed, Followed by Consolidation Therapy):*<br>• Liposomal amphotericin B 3–5 mg/kg body weight, IV once daily (preferred)<br>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative)<br><br>*Consolidation Therapy (Followed by Chronic Suppressive Therapy):*<br>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for 12 months<br><br>Central Nervous System Infection<br>*Acute Therapy (4–6 Weeks, Followed by Consolidation Therapy):*<br>• Liposomal amphotericin B, 5 mg/kg body weight IV once daily **(AII)**<br><br>*Consolidation Therapy (Followed by Chronic Suppressive Therapy):*<br>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for ≥12 months and until histoplasma antigen is no longer detected in cerebrospinal fluid | mg) per dose, twice daily (maximum 600 mg/day) for 12 months<br><br>Moderately Severe to Severe Disseminated Disease:<br>• If itraconazole not tolerated, amphotericin alone for 4–6 weeks can be used with monitoring that confirms decline in histoplasma urine and serum antigen levels.<br>• Liposomal amphotericin B 3–5 mg/kg body weight IV once daily (preferred) for 4–6 weeks<br>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) for 4–6 weeks | exceeding 10 µg/mL should be followed by dose reduction.<br><br>High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered.<br><br>Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy.<br><br>Amphotericin B deoxycholate is better tolerated in children than in adults. Liposomal amphotericin B is preferred for treatment of parenchymal cerebral lesions. |

**Key to Acronyms:** cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system; IV = intravenous

# 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)**.<br>• Ideally, HPV vaccine should be administered before an individual becomes sexually active **(AIII)**.<br>• 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.<br>• Sexually active female adolescents who are HIV-infected should have routine cervical cancer screening whether or not they have been vaccinated **(AIII)**.<br>• 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)**.<br>• If the results of the Pap smear are abnormal, in general, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by the American Society for Colposcopy and Cervical Pathology (http://www.asccp.org/ConsensusGuidelines/tabid/7436/Default.aspx).<br>• 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)**.<br>• 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)**.<br>• 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)**.<br>• Genital warts should be treated per the 2010 Centers for Disease Control and Prevention STD treatment guidelines (located at http://www.cdc.gov/std/treatment/2010/) |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>*† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents* |

## Epidemiology

The majority of human papillomaviruses (HPV) fall predominantly into the alpha HPV genus. Alpha HPV infects cutaneous and mucosal squamous epithelium. More than 100 distinct types of alpha HPV exist.[1] HPV can be detected on normal healthy mucosal and cutaneous surfaces but also is associated with warts and anogenital pre-cancers and cancers and oropharyngeal cancers in adults, and in rare cases, in adolescents and children. Certain types are found predominantly in cutaneous warts (such as HPV2) whereas other distinct mucosal types are associated with anogenital and oropharyngeal cancers. The mucosal HPV types found in cancers are referred to as high-risk and those not associated with cancers are referred to as low-risk types. Of the approximately 40-plus genital (i.e., mucosal) HPV types, 12 types have been established as high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), and 6 as probable high-risk (26, 53, 66, 68, 73, 82).[1] HPV16 alone accounts for 50% of all squamous cell (SC) cervical cancers and 80% to 90% of all SC anal cancers. Of the HPV-associated vulvar, vaginal, penile, and oropharyngeal cancers, HPV16 is attributed to 50% to 80% as well.[2-4]

Skin warts associated with HPV are common in children,[5-7] whereas mucosal warts, including anogenital[8,9] and oral warts, are less common.[10]

HPV-associated cutaneous warts are transmitted by close person-to-person contact that is facilitated by minor trauma to the skin. Skin warts are most commonly associated with cutaneous HPV types 1, 2, 3, 4, 27, and 57, and are associated with distinct wart histology. The estimated prevalence of skin warts in immunocompetent children varies by population from approximately 5% to 50%.[5-7] In comparison, children with compromised cellular immunity often have intense and widespread appearance of both cutaneous and mucosal warts. Unfortunately, no data are available on prevalence or incidence of skin warts in HIV-infected children.

HPV-associated anogenital warts are known to be transmitted by sexual contact, thereby raising the concern of sexual abuse when diagnosed in pre-pubertal children.[9,11] The prevalence of HPV-associated anogenital warts varies by population and risk factors, For example, varying prevalences of HPV-associated anogenital warts have been reported in children; 0% in non-abused pre-pubertal children,[8] 1.7/1000 in children referred to a tertiary care hospital[9] and 1.8% in children with suspected sexual abuse.[12] Several studies have shown that anogenital warts can be found in children with no evidence of sexual abuse, suggesting that transmission may occur through other means such as perinatally[13] or through other non-sexual means (e.g., autoinoculation or transmission from the hands or mouth of a caretaker).[14-16] HPV6 and 11 are the most common types detected in anogenital warts in children.[17] In one study of children with anogenital warts, 24% of children had an adult family member with anogenital warts, 63% had a mother with cervical intraepithelial neoplasia (CIN), and 48% had a family member with extra-genital warts,[18] suggesting non-sexual transmission as the route of infection.[19] Rarely, cutaneous HPV types also have been associated with anogenital warts in children.[20] Oral papillomas also have been described in children as well as sexually active adolescents and are commonly associated with HPV6 and 11. Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP), which is also associated with HPV6 and 11, can be life-threatening due to the ability of the lesions to cause airway obstruction. Incidence of JORRP in the United States is around 1.7 to 4.3 per 100,000.

Detection of HPV DNA in normal tissue of infants has been documented, suggesting that perinatal transmission also can occur. Rates of HPV DNA detected in newborns vary significantly (0%–70%), and when found in the infant, concordance between the mother and infant also is quite variable (<1%–100%).[21-23] Studies completed before 2000 tended to have higher rates of detection, whereas more recent studies find low rates of HPV DNA detected in infants (<5%). A systematic quantitative review of maternal-neonatal transmission concluded that pooled mother-to-child HPV transmission was around 6.5%.[21] Several authors have suggested that the rate of HPV detection in infants depends on the rate found in pregnant mothers.[22,24] Risks of DNA detection in newborns include mother's HPV status at delivery and presence of anogenital lesions (i.e., condyloma or squamous intraepithelial lesion [SIL]) in the mother.[22,23] Recent studies have concluded that pregnancy itself, even in HIV-infected women, is not associated with increased vulnerability to HPV.[25]

In a recent study, 19.7% of infants born to HPV-infected mothers and 16.9% of infants born to mothers who were HPV-negative at delivery were found to be HPV-positive in their orogenital area at some time during a 14-month follow-up period, suggesting that vertical transmission is not the sole source of oral or genital HPV infection in infants.[22] Although maternal history of condyloma at time of delivery has been a well-described risk factor for appearance of genital condyloma in infants months later, the risk remains quite low, with estimates of 7 per 1,000 births with a maternal history of genital warts.[26] In a parent-child study in Finland,[27] the cumulative detection rates for high-risk HPV from the child's genital and oral samples were 36% and 42%, respectively.[28] However, persistence of HPV was less common, with persistent oral HPV in 10% of infants and persistent genital HPV in 1.5% of infants. Together, these data show that while oral and genital perinatal transmission can occur, persistence is unusual when infection is acquired (whether through vertical or horizontal transmission).

Genital HPV is most commonly a result of sexual transmission. Young age at first sexual intercourse and a higher number of recent sex partners are strong risk factors for HPV in both women and men.[29-34] Prevalence of HPV is common in sexually active adolescent girls, with prevalence of 12% to 64%, compared with 2% to 7% in women aged >35 years.[32,35-37] Cervical HPV is acquired shortly after onset of sexual activity, with 50% cumulative exposure within 3 years,[29,30] even among young women with one sex partner.[38] Recent data on young men suggest similarly high rates of genital HPV acquisition associated with number of sexual partners.[39] Rates of HPV are higher in HIV-infected adolescents and adult women than in HIV-uninfected women.[40-42] As with HPV, CIN and condyloma also are more common in HIV-infected women than uninfected women.[43-47]

Although the incidence of anogenital HPV infection in sexually active youth is high, longitudinal studies have demonstrated that 80% to 90% of infections in HIV-uninfected youth are transient, and spontaneously regress.[48,49] Repeated infections with new types are common,[49] but whether repeat detection of same-HPV-type infections result from new exposures or from reactivation of latent infection is unknown.[50] Rates of clearance of genital HPV infection are even higher in men.[39] Overall prevalence of HPV remains above 50% in men across all age groups, suggesting that repeated infections are even more common in men than in women.[51] A risk for HPV in the anus in women is associated with anal intercourse.[52,53] One study also showed that anal HPV acquisition was associated with cervical HPV infection and was quite common even without reported anal intercourse, suggesting that other sexual and non-sexual routes of anal acquisition are possible.[53]

The higher prevalence of HPV infections in HIV-infected populations may result partly from increased HPV persistence in these patients. In one study of adolescents with HIV, only 50% cleared their HPV infections.[54] Detection of anal HPV also is higher in HIV-infected youth.[55] Receptive anal sex is a risk factor for anal HPV in HIV-infected and HIV-uninfected men;[56] the association between anal HPV infection and anal sex is not as clear for women.[55,57] In studies of HIV-infected and -uninfected women, anal HPV infection is equal to if not more prevalent than cervical infection.[53,58]

Persistent infection with high-risk HPV types is associated with increased risk of CIN and cervical and vulvovaginal carcinoma in women and of anal intraepithelial neoplasia (AIN) and anal carcinoma in both women and men. Rates of HPV-associated cancers including cervical, vulvar, vaginal, penile, anal (men and women), and oropharyngeal are higher in HIV-infected individuals[59-61] and believed to result predominantly from the increased risk of persistent infection in this group. The rates are highest in HIV-infected young people.[59] Adolescent girls, whether HIV-infected or -uninfected, differ biologically from adult women (e.g., increased areas of cervical squamous metaplasia in adolescents, resulting in an increased susceptibility to either persistent infection or disease).[40,62]

Even though combination antiretroviral therapy (cART) has dramatically altered HIV's natural history, its impact on HPV and HPV-associated neoplasia is less clear. Several studies have shown that HPV prevalence and rates of CIN and AIN have not been reduced with cART,[54,63,64] in contrast to rates of Kaposi sarcoma, which have fallen dramatically since the advent of cART. Current data suggest that cervical cancer rates have decreased in most racial/ethnic groups, while anal cancer rates have increased in HIV-infected individuals.[65]

Other risks associated with increasing rates of cervical cancer include lack of cervical cancer screening, prolonged use of hormonal contraception, parity, smoking, and immunocompromising conditions (other than HIV).[31] A recent study of perinatally infected adolescents showed that 30% of HIV-infected girls had an abnormal (atypical squamous cells of undetermined significance [ASC-US] or greater) Pap smear.[66] The mean age at the time of the first Pap smear was 16.7 years (range 13–23 years). The observational study also noted that 23 cases of condyloma were reported in those younger than age 13. In a small study of Brazilian infants, HIV in the mother was noted to be a risk factor for neonatal transmission.[24] These data suggest that perinatally infected children may be more vulnerable to maternal transmission of HPV, because of higher rates of HPV in this group, and higher rates of HPV persistence in the neonatal and infant period due to immunosuppression.

## Clinical Manifestations

### *Genital, Anal, Oral and Skin Warts*

Genital HPV types cause hyperplastic, papillomatous, and verrucous squamous epithelial lesions (warts) on skin and mucus membranes, including anal, genital, oral, nasal, conjunctiva, gastrointestinal, bladder, and respiratory tract mucosa. Lesions in the genital area are often referred to as condyloma accuminata. Warts can be single or present with multiple lesions and often appear as papules, flat, smooth or pedunculated lesions. Common sites for skin warts are the hand, elbows, knees, and feet. JORRP can present with hoarseness and difficulty breathing.

### *Precancerous and Cancerous Lesions*

Genital lesions associated with HPV include high grade CIN; vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), and AIN. Most intraepithelial neoplasias are asymptomatic. Cancers associated with high-risk HPV types include cervical, vulvar, vaginal, penile, anal, and oropharyngeal, specifically at the base of the tongue and tonsils. Cancers are often asymptomatic but also can be associated with bleeding, pain or a palpable mass.

## Diagnosis

### *Genital, Anal, Oral and Skin Warts*

Most cutaneous and anogenital warts can be diagnosed by visual inspection. A speculum examination may be required for cervical and vaginal lesions and anoscopy for intra-anal lesions. If the lesions do not respond to standard therapy or the warts are pigmented, indurated, fixed, or ulcerated, biopsy may be needed.

Patients in whom cancer or JORRP is suspected should be referred to an expert for diagnosis and management.

### *Intraepithelial and Squamous Cell Cancers*

The same cytology and colposcopic techniques used to detect CIN in HIV-uninfected patients should be used in HIV-infected patients. Cytology is a screening test for cervical cancer (see Prevention section). However, histology remains the gold standard for confirming CIN and invasive cancers. In sexually active individuals, the entire genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia or invasive cancers. Vaginal, vulvar, and anal cancers often can be palpated by digital examination of the vaginal, vulvar, and intra-anal regions. Diagnosis is by histology; CIN, AIN, VaIN, VIN, and oral cancer are recognized through visual inspection, which includes colposcopy and high-resolution anoscopy (HRA), and biopsy to confirm diagnosis.

## Role of HPV Testing

HPV DNA can be detected using several platforms.[67] HPV tests available can detect from 2 to 13 to 14 oncogenic HPV types in clinical specimens. Currently, data are insufficient for use of HPV testing in triage of HIV-infected women with abnormal cytology results or for follow-up after treatment **(BIII)**, and it is not recommended for primary screening for any women younger than age 30. HPV testing also is not helpful in diagnosing or managing visible genital, skin or oral warts. HPV testing is not recommended in any circumstance for adolescent girls (aged <20 years),[68] regardless of whether they are HIV-infected or HIV-uninfected, because of the high rates of HPV infection.

## Prevention Recommendations

### *Preventing Exposure*

HIV-infected individuals should use latex condoms during every act of sexual intercourse to reduce the risk of exposure to (or transmission of) sexually transmitted pathogens **(AII)**. Condom use has been shown to reduce HPV genital acquisition, reduce risk of genital warts, and enhance clearance of CIN.[33,69,70] This is true in both HIV-infected men and women.[71] In all circumstances where a male condom cannot be used properly, the use of a female condom may be protective for vaginal intercourse **(AII)**, but may not be protective for anal intercourse involving either women **(BIII)** or men who have sex with men **(BIII)**.[72,73]

## *HPV Vaccine*

The quadrivalent and bivalent vaccines have been shown to prevent HPV16 and 18 infections and associated precancers in females and the quadrivalent has been shown to prevent HPV16 and 18 infections and precancers in males. The quadrivalent vaccine also protects against HPV6 and 11 infections and associated genital warts in females and males.[74-77] Because the HPV vaccine prevents infection and is not therapeutic, it ideally should be administered before potential exposure to HPV through sexual contact **(AIII)**. Data from clinical trials[75] of both vaccines showed that if previous exposure to the vaccine HPV types was documented, no efficacy was noted for that type, underscoring the fact that the vaccine is not therapeutic.

A randomized clinical trial of the quadrivalent HPV vaccine in the United States found the vaccine to be safe and immunogenic in HIV-infected children aged 8 to 11 years.[78] Serum antibodies to HPV6 and 18 were 30% to 50% lower than in historic age-matched immunocompetent controls. In addition, at 18 months after the third dose of vaccine, 94% to 99% had antibody to HPV6, 11, and 16, however, only 76% had antibody to HPV18. This group was also given a fourth dose which demonstrated an excellent amnestic response for all the vaccine associated HPV types.[79] The clinical significance of this observation is unknown. Ongoing studies will continue to evaluate the efficacy and duration of immune response in HIV-infected boys and girls. Although no studies in HIV-infected adolescents and adult women have yet been published, a study in HIV-infected men found the vaccine to be safe and immunogenic.[80]

Data on prior exposure to vaccine types in HIV-positive individuals aged 13 to 26 years are insufficient to determine the proportion that would benefit from vaccination.

HPV vaccination in HIV-infected youth is recommended **(AIII)**. Either bivalent or quadrivalent HPV vaccine offers protection against the two most common types that are associated with HPV-associated genital cancers. Quadrivalent vaccine also offers protection against the two most common types that cause genital warts. Either the bivalent or quadrivalent HPV vaccine is recommended for routine vaccination of HIV-infected females aged 11 to 12 years; quadrivalent HPV vaccine is recommended for routine vaccination of HIV-infected males aged 11 to 12 years.

The first dose of the HPV vaccine series should be administered to males and females aged 11 to 12 years, but can be administered as early as age 9 years. The second dose should be administered 1 to 2 months after the first dose, and the third dose should be administered 6 months after the first dose. HIV-infected adolescents aged 13 to 26 years who have not been previously vaccinated or have not completed the vaccine series should be vaccinated (see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm) **(AIII)**.

## *Preventing Disease*

### Circumcision

There is evidence that circumcision reduces the rates of oncogenic HPV infection of the penis,[81-85] and is associated with lower risk of penile cancer[86,87] and cervical cancer in sexual partners.[88] Because other studies suggest no benefit,[89] evidence is insufficient to recommend adult male circumcision solely for the purpose of reducing the risk of oncogenic HPV infection in HIV-infected men or their sex partners in the United States, or infant male circumcision solely for the purpose of reducing the future risk of oncogenic HPV infection before or after they initiate sex.

## *Preventing Cervical Cancer*

HIV-infected adolescents and women 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)**. Because of the reportedly high rate of progression of abnormal cytology in HIV-infected adolescents[46] and young women who were infected through sexual intercourse, providers should consider screening within 1 year of onset of sexual activity, regardless of age or method of HIV acquisition **(BIII)**. Although no similar prospective data are available for perinatally infected adolescents, Brogly et al[66] reported that 30% of perinatally infected adolescents had an abnormality (ASCUS or greater ) on their first Pap smear. HIV-infected adolescents and women who have become sexually active, whether vaccinated or not, should continue screening annually throughout their lives **(BIII)**. Evidence is insufficient to recommend cervical cancer screening in HIV-infected girls who are not sexually active.

If Pap smear results are abnormal, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by American Society for Colposcopy and Cervical Pathology.[68] Exceptions include the role of HPV testing in women age 21 and older (see section HPV Testing above). It is recommended that triage be done in HIV-infected adolescents similar to that in adult women, in that any SIL, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells cannot exclude a high-grade lesion (ASC-H) should be referred for colposcopy **(BIII)**. For ASC-US, either immediate referral to colposcopy or repeat cytology in 6 to 12 months is recommended. Some clinicians may opt for colposcopy in HIV-infected adolescents/women. If ASC-US or greater is found on repeat cytology, referral to colposcopy is warranted.

### *Preventing Vaginal and Vulvar Cancer*

No routine screening for vaginal or vulvar cancer is recommended for HIV-infected children and adolescents. Women with a history of high-grade CIN or invasive cervical cancer are at increased risk of vulvar and vaginal cancer and should be referred to a specialist **(AIII)**.

### *Preventing Anal Cancer*

At this time, no national recommendations exist for routine screening for anal cancer; some specialists recommend anal cytologic screening for HIV-seropositive men and women **(CIII)**.[69] An annual digital anal examination may be useful to detect on palpation masses that could be anal cancer **(BIII)**.[90] If anal cytology is performed and indicates ASC-US, ASC-H, LSIL, or HSIL, then it should be followed by HRA **(BIII)**. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer **(BIII)** (see section on treatment for details of treatment of AIN).

## Treatment Recommendations

### *Treating Disease*

#### Genital Warts

Multiple treatments for HPV-associated skin and external genital lesions exist, but no one treatment is ideal for all patients or all lesions **(CIII)**.[91] Treatment can induce wart-free periods, but the underlying viral infection can persist, resulting in recurrence. Treatment modalities for external genital warts are the same for HIV-infected and -uninfected populations. Guidelines for the treatment of warts found in the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2010, should be followed.[92] Individuals who are immunosuppressed because of HIV may have larger or more numerous warts, and may not respond as well as immunocompetent individuals to therapy for genital warts. Recurrences after therapy also are an issue for these patients.[92-95] Topical treatments may be ineffective in patients with large or extensive lesions. Self-applied therapies include podofilox (0.5%) solution or gel, imiquimod (5%) cream, and sinecatechin ointment. Provider-applied agents include trichloroacetic or bichloroacetic acid (TCA; BCA) (80%–90% aqueous solution).

Other treatments include intralesional interferon-alfa (IFN-α) or 5-fluorouracil [5-FU]/epinephrine gel implant, and cidofovir topical gel (1%). Cidofovir gel (1%) is a topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection **(CIII)**. Topical cidofovir can be absorbed systemically and associated with renal toxicity.[96] Injectable therapy (such as with IFN-α or 5-FU/epinephrine gel implant) should be offered in only severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects.

Lesions can be removed by cryotherapy or surgery **(BIII)**. Cryotherapy (application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1 to 2 weeks up to 4 times. The major toxicity is local pain. Adequate local pain management is essential for all caustic treatments. Topical anesthetics are favored. Lesions can be removed surgically by tangential scissor, tangential shave excision, curettage, or electrosurgery.

Limited data are available on treatment of oral warts in HIV-infected patients. Limited lesions can be treated with provider-applied therapies such as TCA or BCA or surgical excision. Extensive lesions should be referred to an expert.[97]

### Treatment of Histologically Confirmed CIN

HIV-infected female adolescents should be evaluated by a clinician with experience in colposcopy and treatment of cervical cancer precursors, and managed according to The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.[68] Not only is progression of lesions more common in HIV-infected women, recurrence is also more common, thus close observation as outlined in the CDC Sexually Transmitted Diseases Treatment Guidelines, 2010, should be considered for management of CIN1 and 2. Follow-up with annual cytologic assessment is recommended for adolescents with CIN1 **(AII)**.[68] At the 12-month follow-up, only adolescents with HSIL or greater on repeat cytology should be referred back to colposcopy. At the 24-month follow-up, those with an ASCUS or greater result should be referred back to colposcopy **(AII)**.

For adolescent girls and young women with a histologic diagnosis of CIN2 or 3 not otherwise specified or cytologic diagnosis of HSIL, either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable, provided colposcopy is satisfactory **(BIII)**.[68] When a histologic diagnosis of CIN2 is specified, observation is preferred, but treatment is acceptable. If compliance with follow-up is a concern, then treatment may be preferable for CIN2. When CIN3 is histologically diagnosed or when colposcopy is unsatisfactory, treatment is recommended **(BIII)**.

If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended **(BIII)**. After 2 consecutive Negative for Intraepithelial Lesion or Malignancy results, adolescents and young women with normal colposcopy can return to routine cytologic screening **(BII)**. Treatment is recommended if CIN3 is subsequently identified or if CIN2 or 3 persists for 24 months **(BII)**.

Persistent CIN1, 2, and 3 lesions in HIV-infected women should be treated as in HIV-uninfected women.[68] Conventional therapies used to treat CIN2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). Excisional methods are recommended for women with abnormal colposcopy and for women with recurrent disease **(AII)**. Recurrence rates of 40% to 60% after treatment have been reported in HIV-infected women undergoing these procedures.[98-100] Management of invasive cervical cancer should follow the National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org).

### Treatment of VIN and Vulvar Cancer and of VaIN and Vaginal Cancer

Treatment of VIN/VaIN should be made in consultation with a specialist. Low-grade VIN/VaIN (VIN 1/VAIN 1) can be observed or managed as per recommendations for vulvovaginal warts. Various treatment modalities for VIN are available, including TCA, local excision, laser vaporization or ablation, and imiquimod therapy. Treatment options for VaIN include topical 5-FU, laser vaporization with a $CO_2$ laser, and excisional procedures with electrosurgical loops or a scalpel excision. Fluorouracil cream and ointments should not be used in pregnant women. Management of invasive vulvar or vaginal cancer should follow the NCCN guidelines (http://www.nccn.org).

### Treatment of AIN

There are no adequate randomized, controlled, therapeutic trials reported for the treatment of AIN. Treatment decisions are based on size, location, and severity of histology. Several different treatments have been described in small open-label studies, including topical 5-FU or imiquimod, infrared coagulation, laser therapy, and surgical excision.[101-104] These data do not indicate that treatment for HIV-infected women with AIN should be modified for patients receiving cART nor is there evidence indicating that cART should be instituted or modified for the purpose of treating AIN.

Treatment of HPV-associated disease at other sites, including oral and penile lesions, does not differ in HIV-infected versus uninfected men and women.

### Role of Antiretroviral Therapy

Severe immunosuppression is associated with greater HPV-associated morbidity and mortality. However, studies show conflicting findings in reducing risk of HPV-related cervical and anal HPV disease, therefore, intraepithelial neoplasia by itself is not an indication for initiating cART.

## *Monitoring of Adverse Events (Including IRIS)*

Monitoring for toxicity and recurrences is required during and after treatment of genital warts. The major toxicity of podofilox, imiquimod, and sinecatechin ointment is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major toxicities of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major toxicities associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional IFN-α can be associated with systemic toxicities of IFN-α, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation may lead to bleeding and abscess formation. Scarring can occur with any of the above treatment modalities. Topical cidofovir may result in systemic absorption and be associated with renal toxicity.[96]

Secondary infections are not uncommon if ulcerations occur, and close monitoring post-treatment for treatment-related toxicity is warranted. Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, post-operative hemorrhage, infection, and cervical stenosis. Treatment of AIN is associated with adverse events, including ulcerations, abscesses, fissures, and fistulas.

An immune reconstitution-like syndrome related to HPV-associated oral warts in HIV-infected adults has been observed in which occurrence of oral warts was associated with decreased HIV RNA levels with cART.[105] Immune reconstitution in response to viral load reduction may result in a return of marked inflammatory responses against latent oral HPV infection. Some studies,[105,106] but not others,[107] have reported an increase in oral warts following cART initiation.

## *Preventing Recurrence*

Monitoring after therapy for cervical disease should follow the ASCCP guidelines.[108] No recommendations exist for preventing recurrence of external genital warts. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions **(AI)**.[90,109]

## *Managing Treatment Failure*

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, re-treatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed **(AIII)**. Genital warts often require more than one course of treatment. Recalcitrant warts should be managed by experienced clinicians and referred for excisional therapy. Recurrence of CIN may require additional treatments (e.g., LEEP, laser). Excisional therapy is recommended for recurrent lesions. Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to the ASCCP guidelines.[68] There is no consensus on the treatment of biopsy-proven recurrent VIN, VaIN or AIN. Risk of recurrence of CIN and cervical cancer after conventional therapy is increased in HIV-infected women, and patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)**.[99,110]

### *Discontinuing Secondary Prophylaxis*

Not applicable.

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## Dosing Recommendations for Prevention and Treatment of Human Papillomavirus (HPV)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis** | HPV vaccine | N/A | See Figure 2 for detailed vaccine recommendations. |
| **Secondary Prophylaxis** | N/A | N/A | N/A |
| **Treatment** | • Podofilox solution/gel (0.5%) applied topically BID for 3 consecutive days a week up to 4 weeks (patient applied). Withhold treatment for 4 days and repeat the cycle weekly up to 4 times **(BIII)**<br>• Imiquimod cream (5%) applied topically at night and washed off in the morning for 3 non-consecutive nights a week for up to 16 weeks (patient applied) **(BII)**<br>• TCA or BCA (80%–90%) applied topically weekly for up to 3 to 6 weeks (provider applied) **(BIII)**<br>• Podophyllin resin (10%–25% suspension in tincture of benzoin) applied topically and washed off several hours later, repeated weekly for 3 to 6 weeks (provider applied) **(CIII)**<br>• Cryotherapy with liquid nitrogen or cryoprobe applied every 1–2 weeks **(BIII)**<br>• Surgical removal either by tangential excision, tangential shave excision, curettage, or electrosurgery | • Intralesional IFN-α is generally not recommended because of high cost, difficult administration, and potential for systemic side effects **(CIII)**<br>• Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults that is commercially available through compounding pharmacies and has very limited use in children; systemic absorption can occur **(CIII)**.<br>• 5-FU/epinephrine gel implant should be offered in only severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects. | Adequate topical anesthetics to the genital area should be given before caustic modalities are applied.<br>Sexual contact should be limited while solutions or creams are on the skin.<br>Although sinecatechins (15% ointment) applied TID up to 16 weeks is recommended in immunocompetent individuals, data are insufficient on safety and efficacy in HIV-infected individuals.<br>cART has not been consistently associated with reduced risk of HPV-related cervical abnormalities in HIV-infected women.<br>Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removing all disease.<br>For women who have exophytic cervical warts, a biopsy to exclude HSIL must be performed before treatment.<br>Liquid nitrogen or TCA/BCA is recommended for vaginal warts. Use of a cryoprobe in the vagina is not recommended.<br>Cryotherapy with liquid nitrogen or podophyllin resin (10%–25%) is recommended for urethral meatal warts.<br>Cryotherapy with liquid nitrogen or TCA/BCA or surgical removal is recommended for anal warts.<br>Abnormal Pap smear cytology should be referred to colposcopy for diagnosis and management. |

**Key to Acronyms:** 5-FU = 5-fluorouracil; BCA = bichloroacetic acid; BID = twice daily; cART = combination antiretroviral therapy; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; IFN-α = interferon alfa; TCA = trichloroacetic acid; TID = three times daily

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

| Panel's Recommendations |
| --- |
| I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of isosporiasis (cystoisosporiasis)? |
| • 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). |
| II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat isosporiasis (cystoisosporiasis)? |
| • 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). |
| III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of isosporiasis (cystoisosporiasis)? |
| • 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). |
| IV. In children with HIV infection receiving secondary prophylaxis for isosporiasis (cystoisosporiasis), when can secondary prophylaxis be safely discontinued? |
| • Clinicians may consider discontinuing secondary prophylaxis in patients without evidence of active Isospora infection who have sustained improvement in immunologic status (CDC immunologic category 1 or 2) for >6 months in response to ART (weak, very low). |
| Rating System |
| *Strength of Recommendation:* Strong; Weak |
| *Quality of Evidence:* High; Moderate; Low; or Very Low |

## Introduction/Overview

## Epidemiology

*Isospora belli (Cystoisospora belli)* is an intestinal coccidian parasite in the phylum Apicomplexa. It was first linked with human disease in 1915 and is believed to infect only humans.[1] Isosporiasis, also known as cystoisosporiasis, occurs worldwide but is more prevalent in tropical and subtropical regions; it has been reported as an etiologic agent of traveler's diarrhea.[2-4] Before the availability of combination antiretroviral therapy (ART), the prevalence of isosporiasis among adults with AIDS was reported to be 15% in Haiti but <0.2% in the United States.[1,5] In several more recent studies from India, *Isospora* was detected in a range of 16% to 47% of patients with HIV with diarrhea.[6-9] In two of the studies, 50% and 81.8% of individuals with *Isospora* infection had CD4 T lymphocyte (CD4) counts <200 cells/mm$^3$.[8,9]

Infected individuals pass noninfective, unsporulated (immature) oocysts in their stool. The oocysts must sporulate (mature) outside the host, in favorable environmental conditions, to become infective.[1,4] Therefore, direct person-to-person transmission of *Isospora* is unlikely. Infection results from ingestion of sporulated oocysts, such as in contaminated food or water. In the proximal small intestine, the ingested oocysts release sporozoites that invade the intestinal epithelial cells. Asexual and sexual stages of the parasite are found in the intestine, and unsporulated oocysts are shed in stool.[1,10]

## Clinical Manifestations

Based on limited data, the incubation period averages approximately 1 week but may range from several days to ≥2 weeks; symptom onset may be acute or insidious.[1,2,4,5] The most common symptom is watery (non-bloody) diarrhea, which can be profuse and result in dehydration, weight loss, and malabsorption. Affected people also can have crampy abdominal pain, flatulence, nausea, vomiting, anorexia, and low-grade fever. Biliary disease (cholecystitis/cholangiopathy) and reactive arthritis also have been reported.[11,12] Whereas immunocompetent hosts typically have self-limited infection, chronic and debilitating diarrhea is common in patients with uncontrolled HIV.

## Diagnosis

Isosporiasis is diagnosed by identifying *I. belli* oocysts in stool (or duodenal aspirates using the Entero-Test) or developmental stages of the parasite in biopsy specimens (e.g., of the small intestine). *I. belli* oocysts are relatively large (23–33 µm long by 10–19 µm wide) but may be difficult to find. Oocysts may be shed in low numbers even by individuals who have severe diarrhea, which underscores the value of repeated stool examinations and use of methods that concentrate and highlight the parasite. Although staining is frequently variable, the organism can be identified with use of a modified acid-fast stain, staining bright red on a green background.[5,10] The organism also autofluoresces when viewed by ultraviolet fluorescence microscopy.[1] Blunting and clubbing of villi and hypertrophied crypts can be seen in small bowel biopsy specimens. There also may be an increase in lymphocytes, plasma cells, and eosinophils in the lamina propria.[10] Peripheral eosinophilia occurs in up to half of patients. Serologic tests are not available. Polymerase chain reaction is a promising diagnostic tool but is not yet commercially available in the United States.[13]

## Prevention Recommendations

### *Preventing Exposure*

Avoiding food or water that might be contaminated with stool may help prevent infection. Careful hand washing and thorough washing of fruits and vegetables are recommended. Hands should be washed with soap and warm water after using the toilet or changing diapers and before handling food.

### *Preventing First Episode of Disease*

There are no U.S. recommendations for primary prophylaxis of isosporiasis. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX, 160 mg and 800 mg of TMP and SMX, respectively) was effective in preventing isosporiasis in adults with World Health Organization stage 2 or 3 HIV infection in Cote d'Ivoire.[14] In addition, in an observational study, the incidence of isosporiasis decreased after widespread availability of ART, except among persons with CD4 counts <50 cells/mm$^3$.[15]

Although studies in children are lacking, the relationship between severe immunosuppression and disease in adults suggests that initiating ART in children with HIV before they become severely immunodeficient may reduce the incidence of isosporiasis.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

TMP-SMX is the recommended treatment for isosporiasis. Three studies performed among adults with HIV in Haiti who were not receiving ART have demonstrated the effectiveness of various TMP-SMX regimens.[5,16,17] In the first study, TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) was administered 4 times daily for 10 days and then twice daily for 3 weeks. In all 15 patients, diarrhea and abdominal pain resolved within 2 days of starting treatment, but 7 patients had recurrent symptoms within a mean of 8 +/- 5.8 weeks following completion of therapy.[5] In the second study, TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) was administered 4 times daily for 10 days; participants were then randomized to 1 of 3 secondary prophylaxis arms. At the completion of the initial 10 days of TMP-SMX therapy, all 32 participants had resolution of diarrhea and abdominal pain and negative stool samples.[16] In the third study, participants were randomized to receive either TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) twice daily for 7 days. TMP-SMX treatment was associated with cessation of diarrhea in all 10 patients and negative results on stool examination at day 7 in 9 of the 10 participants, while ciprofloxacin was associated with resolution of diarrhea in 10 of 12 participants and negative stool examinations in 9 of the 12 participants.[17] On the basis of these studies in adults, the recommended treatment for children with HIV is TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Daily pyrimethamine (50–75 mg in adults), with folinic acid (10–25 mg/day) to prevent myelosuppression, may be an effective therapy and is the traditional treatment alternative for patients who are intolerant of TMP-SMX.[18] Other potential agents to consider for TMP-SMX-intolerant patients include ciprofloxacin or nitazoxanide. Data from a randomized, controlled clinical trial described above[17] show that ciprofloxacin is less effective than TMP-SMX; limited data are available about use of nitazoxanide for treatment of isosporiasis.[19,20]

As with all cases of diarrhea regardless of the cause, supportive care, including replenishment of fluids and electrolytes, is essential.

## *Monitoring and Adverse Events (Including IRIS)*

Immune reconstitution inflammatory syndrome has not been reported in association with treatment of isosporiasis. In general, recommended treatment regimens are well-tolerated.

## *Managing Treatment Failure*

If symptoms worsen or persist, the frequency of the TMP-SMX dose may be increased to 3 to 4 times daily and/or the duration of treatment lengthened up to 3 to 4 weeks.[5,21] Alternative agents (ciprofloxacin or nitazoxanide) can also be tried. Limited data regarding treatment outcomes are available for albendazole,[22-24] doxycycline,[25] roxithromycin,[26] and spiramycin.[27]

## *Secondary Prevention*

The relationship between the use of ART and recovery from isosporiasis remains unknown. However, because the incidence of isosporiasis has been reported to be higher in more severely immunosuppressed patients,[15] it seems reasonable that initiation of ART in children with isosporiasis who are not already receiving ART to attempt to improve immunologic status may be effective in decreasing the risk of relapse.

Following treatment of an acute episode of isosporiasis, secondary prophylaxis should be administered to patients with severe immunosuppression (Centers for Disease Control and Prevention [CDC] immunologic category 3) for an indefinite period until sustained immunologic recovery is observed. Pape et al. randomized adults with HIV who had completed a TMP-SMX treatment course for acute isosporiasis to one of three secondary prophylaxis regimens: TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) three times per week, sulfadoxine (500 mg) plus pyrimethamine (25 mg) once weekly, or placebo.[16] The active regimens in the two treatment arms were both effective in preventing recurrence of diarrhea during the observation period. However, the combination of sulfadoxine and pyrimethamine **is not recommended** in the United States because of increased risk of severe cutaneous reactions. In another study, adult patients with a clinical and microbiologic response to treatment of acute infection with TMP-SMX or ciprofloxacin received secondary prophylaxis for 10 weeks with the same agent used for treatment but at reduced doses: TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) three times per week. Both agents were effective in preventing recurrence during the monitoring period.[17] On the basis of these findings in adults, TMP-SMX, 2.5 mg/kg body weight twice daily of the trimethoprim component, administered 3 days per week, either on three consecutive days (e.g., Monday, Tuesday, and Wednesday) OR on an alternating-day schedule (e.g., Monday, Wednesday, and Friday) is recommended for secondary prophylaxis in children with HIV. Patients intolerant of TMP-SMX may receive pyrimethamine (plus folinic acid) as secondary prophylaxis.[18] Ciprofloxacin three times weekly can also be considered as a second-line alternative.

### *Discontinuing Secondary Prophylaxis*

There are no data to provide guidance regarding the optimal duration of secondary prophylaxis. All patients should be monitored for recurrence, and severely immunosuppressed patients may benefit from receiving secondary prophylaxis indefinitely. However, secondary prophylaxis probably can be discontinued in patients without evidence of active *I. belli* infection who demonstrate sustained recovery from severe immunosuppression. In adults, a CD4 count >200 cells/mm$^3$ for >6 months is recommended before discontinuing secondary prophylaxis. In children, a reasonable time to discontinue secondary prophylaxis would be after sustained improvement in CD4 count or CD4 percentage from CDC immunologic category 3 to 1 or 2.

## Recommendations

### *Primary Prevention*

**I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of isosporiasis (cystoisosporiasis)?**

- 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)**.

  Because isosporiasis results from ingestion of sporulated oocysts, such as in contaminated food or water, careful handwashing and washing of fruits and vegetables are recommended.

### *Treatment*

**II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat isosporiasis (cystoisosporiasis)?**

- Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in children with HIV infection **(strong, high)**.

  Three studies conducted among adults with HIV infection in Haiti demonstrated the efficacy of TMP-SMX for treatment for isosporiasis. In two of these studies, initial therapy with TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) 4 times daily for 10 days was effective in reducing diarrhea and abdominal pain.[5,16] In the third study, participants were randomized to receive either TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) twice daily for 7 days.[17] TMP-SMX treatment resulted in cessation of diarrhea in all 10 participants and negative results on stool examination at day 7 in 9 of the 10 participants, while ciprofloxacin resulted in resolution of diarrhea in 10 of 12 participants and negative stool examinations in 9 of the 12 participants. On the basis of these studies in adults, the recommended treatment for children with HIV infection is TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days.

- Supportive care, including replenishment of fluids and electrolytes, should be provided **(expert opinion)**.

  There are no studies that address this specific management issue in isosporiasis. However, recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.

## *Secondary Prevention*

**III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of isosporiasis (cystoisosporiasis)?**

- Combination 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 an observational study, the incidence of isosporiasis decreased after widespread availability of ART, except among persons with CD4 counts <50 cells/mm$^3$.[15] Although data in children are lacking, the relationship between severe immunosuppression and disease in adults suggests that initiation of ART in children with HIV infection may help prevent recurrence of isosporiasis.

- In children with severe immunosuppression, treatment of isosporiasis should be followed by secondary prophylaxis with TMP-SMX **(strong, high)**.

  Two randomized clinical trials among adults with HIV infection in Haiti demonstrated that secondary prophylaxis with TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively, three times per week) following 10 days of initial treatment, was effective in preventing relapse during the monitoring period.[16,17] On the basis of these findings in adults, TMP-SMX, 2.5 mg/kg body weight twice daily of the trimethoprim component, administered 3 days per week, is recommended for secondary prophylaxis for children with HIV infection.

**IV. In children with HIV infection receiving secondary prophylaxis for isosporiasis (cystoisosporiasis), when can secondary prophylaxis be safely discontinued?**

- Clinicians may consider discontinuing secondary prophylaxis in patients without evidence of active *Isospora* infection who have sustained improvement in immunologic status (CDC immunologic category 1 or 2) for longer than 6 months in response to ART **(weak, very low)**.

  There are no clinical trials demonstrating the optimal duration of secondary prophylaxis for isosporiasis. However, the observation that improved immunologic status associated with ART reduced the incidence of infection[15] and recommendations for other opportunistic infections suggest that secondary prophylaxis can be safely discontinued when sustained improvement in immunosuppression is demonstrated.

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## Dosing Recommendations for Prevention and Treatment of Isosporiasis (Cystoisosporiasis)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Prophylaxis | There are no U.S. recommendations for primary prophylaxis of isosporiasis. | N/A | Initiation of ART to avoid severe immunodeficiency may reduce incidence; TMP-SMX prophylaxis may reduce incidence. |
| Secondary Prophylaxis | If Severe Immunosuppression:<br>• TMP-SMX 2.5 mg/kg body weight of the TMP component (maximum 80 mg TMP) twice daily by mouth 3 times per week | Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid 5-15 mg by mouth once daily.<br>Second-Line Alternative:<br>• Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth 3 times per week | Consider discontinuing secondary prophylaxis in patients without evidence of active Isospora infection who have sustained improvement in immunologic status (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for >6 months in response to ART.<br>In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no data exist for dosing in children. Thus, the recommended dose for secondary prophylaxis in children is pyrimethamine 1 mg/kg (maximum 25 mg) by mouth once daily.<br>Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues. |
| Treatment | TMP-SMX 5 mg/kg body weight of the TMP component (maximum 160 mg TMP) twice daily by mouth for 10 days | Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid 5-15 mg by mouth once daily for 14 days<br>Second-Line Alternatives:<br>• Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth twice daily for 7 days<br>• Nitazoxanide (see doses below) for 3 consecutive days<br>*Children Aged 1 Year–3 Years:*<br>• Nitazoxanide 100 mg by mouth every 12 hours<br>*Children Aged 4 Years–11 Years:*<br>• Nitazoxanide 200 mg by mouth every 12 hours<br>*Adolescents Aged ≥12 Years and Adults:*<br>• Nitazoxanide 500 mg by mouth every 12 hours | If symptoms worsen or persist, the TMP-SMX dose (5 mg/kg/dose of the TMP component) may be given more frequently (e.g., 3–4 times daily by mouth for 10 days) and/or the duration of treatment may be increased to 3–4 weeks.<br>The optimal duration of treatment with pyrimethamine has not been established.<br>Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues. |

Key to Acronyms: CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; ART = antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole

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

**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*

## Epidemiology

Malaria is caused by the obligate, intracellular protozoa of the genus *Plasmodium*, and is transmitted by the bite of an infective female Anopheles mosquito. Worldwide, malaria is a leading killer of children and pregnant women. In the United States, most malaria cases occur in patients who have returned from travels to areas of endemic malaria transmission. Rarely, cases occur as a result of exposure to infected blood products, local mosquito-borne transmission (i.e., autochthonous transmission), or mother-to-child transmission (MTCT) (congenital malaria). Prompt recognition and treatment are essential, and failure to act quickly and appropriately can have grave consequences.

In 2009, 1484 cases of malaria were reported in the United States, of which 4 were fatal.[1] In the majority of cases in which species were identified, *Plasmodium falciparum* was the pathogen involved; however, in 38% of cases, the species was either not reported or unidentified. Lack of adherence to prophylaxis is the key identified risk factor for acquisition of malaria in those for whom data are available.

## High-Risk Groups

United States-born children visiting family in malaria-endemic regions are at highest risk of malaria infection. Children of foreign citizenship, children of unknown resident status, and adopted children who come from countries of endemic malaria transmission are also at high risk. Education regarding the misconception that prior exposure to malaria confers protection against re-infection is important; families should be prepared (with malaria chemoprophylaxis) and educated with travel advice (e.g., such as recommending use of insecticide-treated nets and insect repellants) before returning to endemic areas **(AII)**. Although some parents may assume that their children are protected from disease because of their ethnic background (from high malaria endemic countries),[2,3,4] the converse is true, with patients in this group at high risk because of factors such as visiting private residences, sleeping in homes that lack screens or air conditioning, and having longer visits, all of which contribute to a higher risk of contracting malaria (http://www.cdc.gov/malaria/travelers/vfr.html). Adults living in the United States but born in malaria-endemic areas often believe they are not susceptible to malaria because of naturally acquired immunity. Such acquired immunity develops after age 5 years in people who reside in areas of stable malaria transmission, but it is partial (providing relative protection against disease, not infection), wanes quickly once people are no longer living in malaria-endemic areas, and may not be present in HIV-infected populations with advanced immunodeficiency. Therefore, both adults and children living in the United States who were born in malaria-endemic areas should be prescribed the same prophylaxis as any other patients traveling to malaria-endemic areas.

## Prevention Recommendations

Recommendations for preventing exposure and for primary chemoprophylaxis are identical for HIV-infected and HIV-uninfected individuals (see http://www.cdc.gov/malaria/travelers/index.html). All travelers to malaria-endemic regions should receive pre-travel counseling on appropriate chemoprophylaxis and avoidance of mosquitos **(AII)**.[4,5] Families should be counseled regarding signs and symptoms of malaria and the need for early medical intervention if these signs and symptoms are present. An early appropriate medical evaluation should be completed on all patients returning from a malaria-endemic area who have unexplained fever or other signs or symptoms of malaria.

### *Preventing Exposure*

All travelers should use personal protective measures to prevent mosquito bites when traveling to malaria-endemic areas **(AII)**,[6] including sleeping under an insecticide-treated bed net and wearing clothing impregnated with permethrin (effective for weeks and through several washings, but not dry cleaning). Discussions regarding the routine use of bed nets should be individualized as per specific sleeping arrangements (air-conditioned hotel vs. open windows). Long-acting N,N-Diethyl-meta-toluamide (DEET) mosquito repellents are safe, practical, and effective, and the duration of protection increases with increasing DEET concentrations, plateauing between 30% and 50%. DEET should be applied (by patients or their caregivers when appropriate) to skin, but not to wounds, cuts, irritated areas, the mouth, or hands of young children **(AIII)**. Additional information about other recommended mosquito repellants can be found at http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm.

Depending on the level of risk, it may be appropriate to recommend to travelers no specific interventions, mosquito-avoidance measures only, or mosquito-avoidance measures plus chemoprophylaxis (Centers for Disease Control and Prevention [CDC] Yellow book; http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm). Pregnant women should discuss travel to endemic areas with a travel medicine expert.

## *Primary Chemoprophylaxis*

Primary chemoprophylaxis should be prescribed to all individuals traveling to malaria-endemic areas, regardless of ethnicity or prior exposure to or illness with malaria. Antimalarial medications may need special preparation, and some are not easily delivered to children. Therefore, families planning to travel to malaria-endemic areas are advised to visit a travel medicine specialist with training and experience in pediatrics at least 2 weeks before departure **(AII)**. If that is not possible, families can still see a travel medicine specialist up to the day of departure, because some antimalarial prophylaxis regimens can still be prescribed and effectively used even at that late date.

For patients traveling to areas with chloroquine-sensitive malaria, chloroquine phosphate (5 mg/kg body weight base, up to 300-mg base) given once weekly is acceptable. Other acceptable choices include primaquine, atovaquone/proguanil, doxycycline, and mefloquine. For travelers to areas with mainly *Plasmodium vivax*, primaquine is a very good option. Travellers who will be given primaquine should have glucose-6-phosphate dehydrogenase (G6PD) testing before this medication is started. Travelers to areas with chloroquine-resistant malaria should take atovaquone/proguanil daily (dosed on a sliding scale by weight bands), or daily doxycycline (2.2 mg/kg body weight for children aged ≥8 years) or weekly mefloquine, dosed based on weight. Medications for prophylaxis should be started before leaving and continued after returning from travel, as per their specific schedule. Trimethoprim-sulfamethoxazole (TMP-SMX) is not a surrogate for antimalarial prophylaxis, and **is not recommended** as effective prophylaxis for malaria **(AIII)**. Although TMP-SMX prophylaxis appears to reduce episodes of clinical malaria to varying degrees, with the already almost universal resistance to sulfadoxine pyrimethamine, it is extremely unlikely that TMP-SMX would be useful alone as primary prophylaxis.[7]

## *Discontinuing Primary Prophylaxis*

Travel-related chemoprophylaxis with chloroquine, mefloquine, or doxycycline usually should be continued for 4 weeks after departure from a malaria-endemic area because these drugs are not effective against malarial parasites developing in the liver and kill the parasite only once it has emerged to infect the red blood cells. Atovaquone-proguanil and primaquine may be discontinued 1 week after departure from malaria-endemic areas.

## *Clinical and Laboratory Manifestations*

HIV increases the frequency and severity of clinical malaria episodes in more severely immunosuppressed adults, pregnant women, and older children, possibly reflecting HIV-mediated interference with acquisition of malaria immunity, but not related to failure of initial antimalarial therapy.[7,8] In young children, there is no clear evidence that HIV infection is associated with more severe malaria disease, although one case-control study in Uganda found an association between HIV infection and cerebral malaria in children.[9]

In a case series of returning travelers, symptoms most commonly reported include fever (100%), headache (100%), weakness (94%), profuse night sweats (91%), insomnia (69%), arthralgias (59%), myalgias (56%), diarrhea (13%), and abdominal cramps (8%).[10] Patients may also have pallor, hepatosplenomegaly, or jaundice. Altered consciousness or seizures may indicate progression to severe malaria. Splenic rupture can be a rare presentation of malaria, requiring urgent medical and surgical management. Rash, lymphadenopathy, and signs of pulmonary consolidation are not characteristic of malaria. Laboratory values may include anemia; high, normal, or low neutrophil counts; normal or low platelets; low sodium (usually because of syndrome of inappropriate antidiuretic hormone secretion and/or dehydration); lactic acidosis; renal insufficiency, increased creatinine, proteinuria, and hemoglobinuria; and elevated lactate dehydrogenase.[11,12] Severe malaria may present before severe anemia (hemoglobin <7 g/dL) is documented.

Although fever is often the most common clinical presentation of malaria in people coming from areas of endemic malaria transmission, it is not uniformly present in children. Non-specific clinical findings often predominate in children and clinical diagnosis in them can be difficult. Malaria fever patterns in children also often do not follow the classically described tertian or quartan patterns described in adults.[13,14] Children more often present with hepatomegaly, jaundice, or splenomegaly than do adults. They are also more likely to have fever >40°C and may present with febrile convulsions. Laboratory findings may include low serum glucose (seen with falciparum malaria), whereas serum glucose measurements in adults may be normal. Children who have severe malaria also may have concomitant bacteremia/sepsis.[2,11,12] In returning travelers, when children are diagnosed with malaria, their siblings might present with malaria at the same time.[2]

Splenomegaly, fever, and thrombocytopenia are highly specific for malaria in immigrant children and need appropriate evaluation.[13,15] Congenital malaria is rare but should be considered in febrile neonates whose mothers migrated from areas where malaria is endemic; however, empiric therapy should not be administered without a confirmed diagnosis.[13] HIV/malaria coinfection during pregnancy has been shown to have additional detrimental effects on maternal and infant survival and to confer increased risk of MTCT of both HIV and malaria.[16]

## Diagnosis

For early and prompt recognition of malaria, physicians must obtain a complete travel history from every febrile patient and maintain a high index of suspicion for malaria in travelers returning from areas of endemic malaria, remembering that signs and symptoms also can vary depending on chemoprophylaxis and prior partial treatment for malaria (see Table 7 from[17] for list of resources or http://wwwnc.cdc.gov/travel/destinations/list.htm). Children who have recently migrated from regions where malaria is endemic should be evaluated for malarial infection upon arrival and/or if they become ill after arriving in the United States. A Giemsa-stained thick blood smear is the most sensitive smear technique for detecting infection, whereas a thin blood smear is used for determination of parasite species and burden (for an example of malaria parasites on smear, please visit http://www.dpd.cdc.gov/dpdx/HTML/Image_Library.htm). Smear accuracy depends upon proper preparation and interpretation of thick and thin smears by experienced laboratory personnel.[17] Because symptoms can develop before parasitemia is detectable in a non-immune person, the initial blood-smear examination may be misleadingly negative. Blood smears should be obtained every 12 to 24 hours for a total of 3 sets to fully evaluate for malaria; if all 3 sets are negative, the probability of malaria is extremely low. In all patients in whom malaria is suspected, smears should be read immediately. A qualified person who can perform and read smears should always be available, even at off-hours. Every effort should be made to establish a diagnosis before therapy is initiated. However, if severe malaria is strongly suspected and diagnostic interpretation is not readily available, empiric intravenous therapy for presumed *P. falciparum* infection should be initiated, with a blood smear preserved for reading as soon as possible. Consultation and aid in the initial diagnosis, speciation, and treatment plan is available via the CDC Malaria Hotline at (770) 488-7788 (Monday–Friday, 9 a.m.-5 p.m., eastern time. For emergency consultation after hours, call (770) 488-7100, and ask to speak with a CDC Malaria Branch clinician).

Performance of rapid diagnostic tests (RDTs) varies greatly, and only one test (Binax) currently is Food and Drug Administration (FDA)-approved. Such tests may have limited usefulness early in infection because their sensitivity is decreased with lower parasite density (see http://www.wpro.who.int/sites/rdt/who_rdt_evaluation/). However, if microscopy is not immediately available, these tests can be used to aid in establishing a diagnosis of malaria. Microscopy must still be performed on all suspected cases of malaria, despite positive and negative RDTs, for confirmation.

Malaria in the United States is a reportable disease. Directions on case definitions and reporting can be found at http://www.cdc.gov/malaria/report.html.

## Treating Disease

Chemoprophylaxis is not completely effective, and malaria should be included in the differential diagnosis of fever or other signs or symptoms consistent with malaria in anyone who traveled to malaria-endemic areas during the previous 12 months (see http://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/malaria-guidelines-overseas.html#sect2). Malaria medications purchased in sub-Saharan Africa or Southeast Asia may be counterfeit; therefore, the index of suspicion must remain high when evaluating children with fever coming from endemic areas, regardless of prior history of antimalarial therapy.

CDC recommends presumptive treatment for malaria for all refugees and adoptees resettling to the United States from sub-Saharan Africa, including those who were treated for malaria before departing from Africa but who did not receive primaquine for treatment of dormant liver stage forms (hypnozoites) of *Plasmodium ovale* and *P. vivax* infection. These patients remain at risk of developing malaria after arrival in the United States and should be evaluated with a high index of suspicion for malaria. Children with past or current *P. vivax* or *P. ovale* infection should receive treatment with primaquine to eradicate the dormant liver stage, if the drug was not previously administered (see CDC Guidance located at http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf).

Treatment of malaria is based on the disease severity, patient age at onset, parasite species, pregnancy status, and known resistance patterns in the area where the malaria infection was acquired **(AI)**. Drug dosing for pediatric patients must be adjusted for weight, and dosing should never exceed the recommended adult dose. Recommendations for treatment—including drug dosing in HIV-infected children and adolescents with malaria—by species are described below and summarized in Table 1, and can also be found at http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Additional information can be found at http://www.malaria.org/ABOUT%20MALARIA/Treatment%20of%20Malaria-Guidelines%20for%20clinicians%20WHO.pdf for further clinical guidance.

HIV infection status does not affect choice or dosing of antimalarial therapy. However, choice of antimalarial therapy may be affected by interactions between antiretroviral (ARV) and antimalarial drugs; clinicians are urged to evaluate for drug interactions before initiating antimalarial therapy (please see Drug Interactions section below).

### *Unknown Species*

Clinicians should always treat patients who traveled to a region in which chloroquine-resistant *P. falciparum* malaria is present for chloroquine-resistant *P. falciparum* malaria if reliable identification of the malaria species is not possible or the patient is severely ill **(AIII)**.

### *Uncomplicated Malaria*

Uncomplicated malaria is defined by the World Health Organization as "symptomatic infection with malaria parasitemia without signs of severity and/or evidence of vital organ dysfunction."[18] The preferred treatment options for uncomplicated malaria include chloroquine phosphate (if chloroquine-susceptible), atovaquone-proguanil, artemether-lumefantrine, or quinine sulfate plus a second medicine (either tetracycline, doxycycline [in children aged ≥8 years] or clindamycin) (see Dosing Table for details) **(AI)**. Mefloquine also can be used for treatment, but has a higher rate of side effects **(AIII)**. Primaquine also must be administered for radical cure of *P. vivax* and *P. ovale* infection. G6PD deficiency **must** be excluded before first use of primaquine because of the risk of severe hemolytic anemia. Primaquine should not be used in pregnant women because the presence of G6PD deficiency cannot be determined in the unborn child **(AIII)**.

### *Severe Malaria*

Severe malaria is defined as acute malaria "with signs of severity and/or evidence of vital organ dysfunction"[18] and is most often caused by *P. falciparum*, but can also be caused by *P. vivax*. Mixed infections can also occur. These signs, symptoms, and laboratory parameters include diminished consciousness or seizures, respiratory distress (acute respiratory distress syndrome [ARDS], Kussmaul's respiration), prostration, hyperparasitemia (>5%), severe anemia (hemoglobin <7 g/dL), hypoglycemia, jaundice/icterus, renal insufficiency, hemoglobinuria, shock, cessation of eating and drinking, repetitive vomiting, or hyperpyrexia. Cerebral malaria is usually defined by presence of coma (Glasgow coma scale

<11, Blantyre coma scale <3). Severe malaria can present long before hemoglobin goes below the 7 mg/dL threshold because of the hemo-concentrating effects of dehydration.

Patients diagnosed with severe malaria should be treated aggressively with intravenous (IV) antimalarial therapy. The only FDA-approved regimen includes quinidine gluconate plus one of the following: doxycycline, tetracycline, or clindamycin. A promising[19] alternative parenteral therapy is IV artesunate (available under Investigational New Drug protocol from CDC for certain patients meeting criteria). Additional alternative therapies include atovaquone-proguanil, clindamycin, mefloquine, or (for children aged ≥8 years) doxycycline. Treatment with IV quinidine or artesunate should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria treated with quinidine should be given an IV loading dose unless they have received more than 40 mg/kg body weight of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine because of the known complications of quinidine, including widening of the QRS complex and/or lengthening of the QTc interval. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the IV infusion. IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout it.

Exchange transfusion should be considered **(BII)** only for treatment of very severe malaria when children have a parasite density of more than 10% and if complications such as cerebral malaria, ARDS or renal complications exist. The risks of exchange transfusion include fluid overload, febrile and allergic reactions, metabolic disturbances (e.g., hypocalcaemia), red blood cell alloantibody sensitization, blood-borne transmissible infection, and line sepsis.[20-22] The parasite density should be monitored every 12 hours until it falls below 1%, which usually requires the exchange of 8 to 10 units of blood in adults.

### *Malaria Despite Chemoprophylaxis*

Medication used for chemoprophylaxis should not be used as a part of a new treatment regimen in individuals who develop malaria despite taking chemoprophylaxis; rather, treatment with one of the other options is recommended.

## Drug Interactions

There are multiple potential interactions between ARV and antimalarial drugs, but data from HIV-infected children and adults remain limited.[7,23-25] Many antimalarials are metabolized by cytochrome p450 enzymes, while certain non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) either inhibit or induce cytochrome p450 enzymes.[26-28] Tetracyclines have no clinically significant interactions expected with PIs or NNRTIs. Atovaquone is not expected to have any significant interaction with common nucleoside reverse transcriptase inhibitors, although no data are available for proguanil. Ritonavir inhibits quinidine metabolism; therefore, concomitant administration of ritonavir (including co-formulated products like lopinavir/ritonavir that contain ritonavir) and quinidine is not recommended. Replacement of ritonavir in ritonavir-containing cART should be considered. The inhibitory action of ritonavir will still be present for several days after dosing is interrupted; thus, in patients with severe malaria already on ritonavir, artesunate should be considered. Caution is also advised before co-administering quinidine with other PIs (including atazanavir, darunavir, and fosamprenavir).

Other drug-drug interactions exist but have not been studied. The CDC Malaria Hotline is an excellent resource for additional assistance with drug-drug interactions, as are the World Health Organization's Guidelines for the Treatment of Malaria (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf). An interactive web-based resource for checking on drug interactions involving ARV drugs is found at the University of Liverpool website http://www.hiv-druginteractions.org.

**Potential Clinically Relevant Interactions between Antimalarial and Antiretroviral Drugs***

| Antimalarial Drug | Protease Inhibitors | NRTI | NNRTI |
|---|---|---|---|
| **Quinine** | PIs: increase quinine levels | No available data | Efavirenz, Nevirapine: reduces quinine levels |
| **Atovaquone/Proguanil** | Lopinavir/Ritonavir, Atazanavir/Ritonavir: reduces atovaquone and proguanil levels | | Efavirenz: reduces atovaquone and proguanil levels |
| **Mefloquine** | Ritonavir: reduces ritonavir levels | | Efavirenz, Nevirapine: reduces mefloquine levels |
| **Lumefantrine, Halofantrine** | PIs: increase lumefantrine or halofantrine levels, which can prolong QT interval | | Efavirenz, Nevirapine: increases lumefantrine or halofantrine levels, which can prolong QT interval |
| **Amodiaquine plus Artesunate** | | | Efavirenz: increases amodiaquine concentration which can increase hepatic toxicity; do not co-administer |
| **Chloroquine, Pyrimethamine, Sulfadoxine-Pyrimethamine** | Ritonavir: alters anti-malarial drug metabolism, may increase chloroquine levels | | |
| **Sulfadoxine-Pyrimethamine** | | Zidovudine: possibly increases risk of anemia | Nevirapine: possibly increases adverse skin or liver adverse reactions; do not start both drugs simultaneously |
| **Artemisinin** | PIs: alter artemisinin metabolism | | Nevirapine: may decrease artemisinin levels |
| **Dapsone** | Saquinavir: alters dapsone metabolism | | |

**Key to Acronyms:** NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI= protease inhibitor

* Modified from: Flateau, C., G. Le Loup, et al. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect Dis*. 2011. 11(7);541-556.

## *Special Populations*

Because primaquine is not routinely prescribed for immigrants as part of a post-treatment/pre-departure regimen, patients who may have had *P. vivax* or *P. ovale* infection in the past would be at continued risk of developing malaria months to years after arrival in the United States. Presumptive treatment on arrival (preferable) or laboratory screening to detect *Plasmodium* infection is recommended for refugees originating in sub-Saharan Africa who have not received pre-departure therapy with a recommended regimen (see http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/malaria-guidelines-domestic.html).

## *Monitoring and Adverse Events (Including IRIS)*

Severe malaria commonly induces hypoglycemia in children, especially when treated with IV quinine/quinidine because of inhibition of gluconeogenesis and induction of endogenous insulin production. Therefore, monitoring glucose levels and use of a glucose-containing crystalloid solution for fluid maintenance is prudent until IV quinine/quinidine therapy has been completed. Monitoring glucose is especially important for children with altered mental status. Cardiac and intensive-care monitoring is also recommended because IV quinine/quinidine can cause hypotension and widening of the QRS interval. Quinine toxicity, a cluster of symptoms that includes tinnitus, dizziness, disorientation, nausea, visual changes, and auditory deficits, can occur. Many of the adverse events associated with quinine are dose-related, and because of age-related differences in the rate at which quinine is eliminated from the body, the frequency and severity of adverse effects associated with quinine drug products may be lower in children. Tinnitus alone, a common (50%–75%) adverse reaction to both oral and IV quinine, usually resolves after treatment. Use of mefloquine at treatment doses may be associated with neuropsychiatric symptoms. Following antimalarial therapy, HIV-infected children should be monitored closely for hematologic complications (especially anemia and neutropenia), which are more frequent because of both the direct hematologic effects of HIV infection and of HIV treatment with other bone-marrow-suppressive drugs such as TMP-SMX and zidovudine. Immune reconstitution inflammatory syndrome caused by malaria has not been reported.

### *Managing Treatment Failure*

Failure of treatment for *P. falciparum* is uncommon in children who receive a full course of appropriate antimalarial therapy. Patients should be monitored for clinical and laboratory response (thick and thin smear) and for signs of recrudescence after therapy completion. Relapse of *P. vivax* and *P. ovale* can occur from the dormant (hypnozoite) liver form but is less common following primaquine treatment. When treatment failure occurs, malaria speciation should be confirmed, as should the geography of where the malaria was acquired. Retreatment with an appropriate first-line regimen (but not the same regimen as initially used) should be given. Discussion with a Pediatric Infectious Disease specialist or consultation through the CDC malaria hotline is appropriate when complex situations arise.

### *Preventing Recurrence*

Except for re-activation of *P. vivax* and *P. ovale* hypnozoites, malaria once successfully treated does not recur, unless re-exposure and re-infection occur. One or even several episodes of malaria infection does not imply protective immunity, and continued exposure to malaria parasites can result in repeated infection, which should be treated as aggressively as the initial event.

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<table>
<tr><th>Indication</th><th>First Choice</th><th>Comments/Special Issues</th></tr>
<tr><td rowspan="2">Primary Prophylaxis</td><td>
<u>For Travel To Chloroquine-Sensitive Areas</u>:
<ul>
<li>Chloroquine base 5 mg/kg body weight base by mouth, up to 300 mg once weekly (equivalent to 7.5 mg/kg body weight chloroquine phosphate). Start 1–2 weeks before leaving, take weekly while away, and then take once weekly for 4 weeks after returning home</li>
<li>Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home
<ul>
<li>11–20 kg; 1 pediatric tablet (62.5 mg/ 25 mg)</li>
<li>21–30 kg, 2 pediatric tablets (125 mg/ 50 mg)</li>
<li>31–40 kg; 3 pediatric tablets (187.5 mg/ 75 mg)</li>
<li>>40 kg; 1 adult tablet (250 mg/100 mg)</li>
</ul></li>
<li>Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1-2 days before travel, daily while away, and then up to 4 weeks after returning</li>
<li>Mefloquine 5 mg/kg body weight orally given once weekly (max 250 mg)</li>
</ul>
<u>For Areas with Mainly P. Vivax</u>:
<ul>
<li>Primaquine phosphate 0.6 mg/kg body weight base once daily by mouth, up to a maximum of 30 mg base/day. Starting 1 day before leaving, taken daily, and for 3–7 days after return</li>
</ul>
</td><td>
Recommendations are the same for HIV-infected and HIV-uninfected children. Please refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/<br><br>
For travel to chloroquine-sensitive areas. Equally recommended options include chloroquine, atovaquone/proguanil, doxycycline (for children aged ≥8 years), and mefloquine; primaquine is recommended for areas with mainly P. vivax.<br><br>
G6PD screening must be performed prior to primaquine use.<br><br>
Chloroquine phosphate is the only formulation of chloroquine available in the United States; 10 mg of chloroquine phosphate = 6 mg of chloroquine base.
</td></tr>
<tr><td>
<u>For Travel to Chloroquine-Resistant Areas</u>:
<ul>
<li>Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home
<ul>
<li>11–20 kg; 1 pediatric tablet (62.5 mg/ 25 mg)</li>
<li>21–30 kg; 2 pediatric tablets (125 mg/ 50 mg)</li>
<li>31–40 kg; 3 pediatric tablets (187.5 mg/ 75 mg)</li>
<li>>40 kg; 1 adult tablet (250 mg/100 mg)</li>
</ul></li>
<li>Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1–2 days before travel, daily while away, and then up to 4 weeks after returning</li>
<li>Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg)</li>
</ul>
</td><td>
For travel to chloroquine-resistant areas, preferred drugs are atovaquone/proguanil, doxycycline (for children aged ≥8 years) or mefloquine.
</td></tr>
</table>

| Indication | First Choice | Comments/Special Issues |
|---|---|---|
| **Secondary Prophylaxis** | <u>For *P. vivax* or *P. ovale*</u>:<br>• Primaquine 0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily for 14 days after departure from the malarious area | This regimen, known as PART, is recommended only for individuals who have resided in a malaria-endemic area for an extended period of time. Adult dose: 30 mg base (52.6 mg salt) orally, daily for 14 days after departure from the malarious area.<br>http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#1939 |
| **Treatment** | <u>Uncomplicated *P. Falciparum* or Unknown Malaria Species, from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region</u>:<br>• Atovaquone-proguanil (pediatric tablets 62.5 mg/25 mg; adult tablets 250 mg/100 mg), dosed once daily:<br>  • 5–8 kg; 2 pediatric tablets for 3 days;<br>  • 9–10 kg; 3 pediatric tablets for 3 days;<br>  • 11–20 kg; 4 pediatric tablets or 1 adult tablet for 3 days;<br>  • 21–30 kg; 2 adult tablets for 3 days;<br>  • 31–40 kg; 3 adult tablets for 3 days;<br>  • >40 kg; 4 adult tablets for 3 days<br><u>Uncomplicated *P. Falciparum* OR Unknown Malaria Species From Chloroquine-Sensitive Region (See Comments for Link to Resistance Map)</u>:<br>• Chloroquine phosphate: 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2500 mg] = 25 mg/kg body weight chloroquine base)<br><u>*P. vivax, P. ovale, P. malariae, P. knowlesi* (All Areas Except Papua New Guinea, Indonesia; See Comments)</u><br>*Initial Therapy (Followed by Anti-Relapse Therapy for P. Ovale and P. Vivax):*<br>• Chloroquine phosphate 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2500 mg] = 25 mg/kg body weight chloroquine base)<br>*Anti-Relapse Therapy for P. ovale, P. vivax:*<br>• Primaquine 0.5 mg base/kg body weight (max 30 mg base) by mouth once daily for 14 days | For quinine-based regimens, doxycycline or tetracycline should be used only in children aged ≥8 years. An alternative for children aged ≥8 years is clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours. Clindamycin should be used for children aged <8 years.<br>Before primaquine is given, G6PD status **<u>must</u>** be verified. Primaquine may be given in combination with chloroquine if the G6PD status is known and negative, otherwise give after chloroquine (when G6PD status is available)<br>For most updated prevention and treatment recommendations for specific region, refer to updated CDC treatment table available at http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf<br>For sensitive and resistant malaria map: http://cdc-malaria.ncsa.uiuc.edu/<br>High treatment failure rates due to chloroquine-resistant *P. vivax* have been documented in Papua New Guinea and Indonesia. Treatment should be selected from one of the three following options:<br>• Atovaquone-proguanil plus primaquine phosphate<br>• Quinine sulfate plus **<u>EITHER</u>** doxycycline **<u>OR</u>** tetracycline **<u>PLUS</u>** primaquine phosphate. This regimen cannot be used in children aged <8 years.<br>• Mefloquine plus primaquine phosphate |

| Indication | First Choice | Comments/Special Issues |
|---|---|---|
| **Treatment,** continued | Uncomplicated *P. falciparum* or Unknown Malaria Species from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region:<br>• Mefloquine (250-mg tablets only): 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth given 12 hours later<br>• Quinine sulfate 10 mg/kg body weight (maximum 650 mg) per dose by mouth every 8 hours for 3 to 7 days, **plus** Clindamycin 7 mg/kg body weight per dose by mouth every 8 hours for 7 days, **or** doxycycline: 2.2 mg/kg body weight per dose (maximum 100 mg) given by mouth every 12 hours, **or** tetracycline 6–12.5 mg/kg body weight per dose by mouth given every 6 hours (maximum dose: 500 mg per dose given 4 times daily) for 7 days.<br>• Artemether-lumefantrine: 1 tablet = 20 mg Artemether and 120 mg lumefantrine, a 3-day treatment schedule for a total of 6 doses. The second dose follows the initial dose 8 hours later, then 1 dose twice daily for the next 2 days.<br>  • 5 to <15 kg; 1 tablet per dose<br>  • 15 to <25 kg; 2 tablets per dose<br>  • 25 to <35 kg; 3 tablets per dose<br>  • >35 kg; 4 tablets per dose | |
| **Severe Malaria** | • Quinidine gluconate 10 mg/kg body weight IV loading dose over 1–2 hours, then 0.02 mg/kg body weight/ minute infusion for ≥24 hours (Treatment duration: 7 days in Southeast Asia, Oceania, otherwise 3 days)<br>PLUS One of the Following:<br>  • Doxycycline 100 mg per dose by mouth every 12 hours for 7 days; for children <45 kg, use 2.2 mg/kg body weight per dose<br>  OR<br>  • Clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours for 7 days.<br>  OR<br>  • Tetracycline 6–12.5 mg/kg body weight per dose every 6 hours (maximum dose 500 mg per dose given 4 times daily) for 7 days<br>• Artesunate 2.4 mg/kg body weight IV bolus at 0, 12, 24, and 48 hours<br>PLUS One of the Following:<br>  • Doxycycline (treatment dosing as above), or Atovaquone-proguanil (treatment dosing as above), or<br>  • Mefloquine 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth once given 12 hours later, or<br>  • Clindamycin (dosing as above) | Quinidine gluconate is a class 1a anti-arrhythmic agent not typically stocked in pediatric hospitals. When regional supplies are unavailable, the CDC Malaria hotline may be of assistance (see below). **Do not** give quinidine gluconate as an IV bolus. Quinidine gluconate IV should be administered in a monitored setting. Cardiac monitoring required. Adverse events including severe hypoglycemia, prolongation of the QT interval, ventricular arrhythmia, and hypotension can result from the use of this drug at treatment doses.<br>IND: IV artesunate is available from CDC. Contact the CDC Malaria Hotline at (770) 488-7788 from 8 a.m.–4:30 p.m. EST or (770) 488-7100 after hours, weekends, and holidays. Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), clindamycin, mefloquine, or (for children aged >8 years) doxycycline.<br>Quinidine gluconate: 10 mg = 6.25 mg quinidine base.<br>Doxycycline (or tetracycline) should be used in children aged ≥8 years. For patients unable to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline. For children >45 kg, use the same dosing as per adults. For IV use, avoid rapid administration.<br>For patients unable to take oral clindamycin, give 10 mg base/kg loading dose IV, followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as a patient can take oral medication. For IV use, avoid rapid administration.<br>Drug Interactions:<br>• Avoid co-administration of quinidine with ritonavir<br>• Use quinidine with caution with other protease inhibitors. |

**Key to Acronyms:** CDC = Centers for Disease Control and Prevention; G6PD = glucose-6-phosphate dehydrogenase; IND = investigational new drug; IV = intravenous; PART = presumptive anti-relapse therapy

# 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?<br>• Effective antiretroviral therapy (ART) is the primary initial treatment for microsporidiosis in HIV-infected children (strong, very low).<br>• Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (expert opinion).<br>• 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).<br>• Systemic fumagillin (where available), in addition to ART, is recommended for microsporidiosis caused by *E. bieneusi* and *V. corneae* (strong, moderate).<br>• Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia (strong, very low).<br>• Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis due to microsporidia other than *E. bieneusi* and *V. corneae* (expert opinion).<br>II. In HIV-infected children who have been treated for microsporidiosis, when can treatment (secondary prophylaxis) be safely discontinued?<br>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:<br>*Strength of Recommendation:* Strong, weak<br>*Quality of Evidence:* High; Moderate; Low; or Very Low |

## Introduction/Overview

### Epidemiology

Microsporidia are obligate, intracellular, spore-forming organisms that primarily cause moderate to severe diarrhea. They are ubiquitous and infect most animal species. They are classified as fungi and defined by their unique single polar tube that coils around the interior of the spore.[1] Many microsporidia have been reported as pathogens in humans, but *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common microsporidia that cause infection in HIV-infected patients. Other microsporidia, such as *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* spp., *Pleistophora ronneeafiei*, *Vittaforma (Nosema) corneae*, *Mycobacterium africanum*, *Mycobacterium ceylonensis*, *Nosema ocularum*, *Tubulinosema acridophagus*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, and *Anncaliia* (syns *Brachiola/Nosema*) *algerae* also have been implicated in human infections. The organisms develop in enterocytes and are excreted in feces. They are transmitted by the fecal-oral route, including through ingestion of contaminated food or water, and, possibly, through contact with infected animals.[2,3] Vertical transmission from an infected mother to her child has not been demonstrated in humans but it does occur in animals.[3]

Prior to the era of antiretroviral therapy (ART), prevalence rates for microsporidiosis were reported to be as high as 70% in HIV-infected adults with diarrhea.[1,4-6] The role of microsporidiosis in chronic diarrhea was questioned early in the HIV epidemic but is now believed to be causal.[7,8] The incidence of microsporidiosis has declined with the widespread use of effective ART, but it is still observed in HIV-infected individuals who are not receiving effective ART.[9] Among HIV-uninfected individuals, microsporidiosis is increasingly recognized in children, travelers, organ transplant recipients, contact lens wearers, and the elderly.[10]

## Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal (GI) tract infection. Microsporidia-associated diarrhea is intermittent, copious, watery, and non-bloody. It may be accompanied by crampy abdominal pain; fever is uncommon. Chronic severe diarrhea can result in dehydration, malnutrition, and failure to thrive. Microsporidia species have been found to cause disease in multiple other organs besides the GI tract, as well as disseminated disease.[4,11] Different infecting species may result in different clinical manifestations. *E. bieneusi* is associated with malabsorption, diarrhea, pulmonary disease, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, peritonitis, keratoconjunctivitis, sinusitis, osteomyelitis, pulmonary disease, and disseminated disease. *Encephalitozoon* (syn *Septata*) *intestinalis* is associated with diarrhea, cholangitis, dermatitis, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, nephritis, urethritis, cystitis, and disseminated infection. *Nosema*, *Vittaforma*, and *Microsporidium* spp. are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* spp. are associated with myositis. *Trachipleistophora* spp. are also associated with encephalitis, cardiac disease, and disseminated disease.

## Diagnosis

To diagnose microsporidia GI infection, thin smears of unconcentrated stool-formalin suspension or duodenal aspirates can be stained with modified trichrome stain. Microsporidia spores are small (1–5 µm diameter) and ovoid; they stain pink to red with modified trichrome stain and contain a distinctive equatorial belt-like stripe. They can also be visualized with hematoxylin-eosin, Giemsa, and acid-fast staining but are often overlooked because of their small size. Chemofluorescence agents such as chromotrope 2R, calcofluor-white (a fluorescent brightener), or Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.

Urine sediment examination by light microscopy can be used to identify microsporidia spores causing disseminated disease (such as *Encephalitozoonidae* or *Trachipleistophora*). Transmission electron microscopy, staining with species-specific antibodies, or polymerase chain reaction (PCR) (using specific primers) is needed for speciation.

Endoscopic biopsy should be considered for all patients with chronic diarrhea of longer than 2 months duration and negative stool examinations. Touch preparations are useful for rapid diagnosis (i.e., within 24 hours). The organisms can be visualized with Giemsa, tissue Gram stain, calcofluor-white or Uvitex 2B, Warthin-Starry silver staining, or chromotrope 2R.[12] Immunofluorescent antibody assays using monoclonal and/or polyclonal antibodies are also available. Sensitive assays using PCR amplification of DNA sequences extracted from stool or biopsy specimens have been developed for *E. bieneusi*, *E. intestinalis*, *E. hellem*, and *E. cuniculi*[13,14] and can be performed at the Centers for Disease Control and Prevention (CDC).

## Primary Prevention

### *Preventing Exposure*

Because microsporidia are most likely transferred from contaminated water, food, or contact with an infected individual or animal, direct contact should be avoided. Untreated water sources (drinking water that has not been chemically treated, filtered, or boiled to eliminate infectious agents) should also be avoided. Fresh fruit and vegetables should be thoroughly washed or peeled prior to eating. This recommendation is especially important for individuals with severe immunosuppression. Hand-washing after exposure to potentially contaminated material or contact with infected individuals or animals also is recommended.

In a hospital, standard precautions (e.g., use of gloves and hand-washing after removal of gloves) should be sufficient to prevent transmission from an infected patient to a susceptible HIV-infected individual. However, contact precautions should be used in the case of a diapered or incontinent child.

### *Preventing Disease*

No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

Immune reconstitution resulting from ART often results in clearance of microsporidia infections. Effective ART is the primary initial treatment for these infections in HIV-infected children and adults.[15] Interestingly, some protease inhibitors, but not others, may have direct inhibitory activity against microsporidia.[16] Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Albendazole has activity against many species of microsporidia,[17-19] but it is not effective against *Enterocytozoon* infections or *V. corneae*.[20,21] Albendazole, in addition to ART, is recommended for initial therapy of microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae*.

Fumagillin (Sanofi-Synthelabo Laboratories, Gentilly, France) (a water-insoluble antibiotic made by *Aspergillus fumigatus*) and its synthetic analog, TNP-470,[22] have both been used to treat microsporidiosis in animals and humans. In a placebo-controlled study of immunocompromised adults (10 of 12 of whom were HIV-infected adults) with *E. bieneusi* microsporidiosis, fumagillin (20 mg/dose orally 3 times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidia spores, which was not observed in placebo recipients.[23] Placebo recipients received fumagillin at the conclusion of the trial and all 6 demonstrated clearance of microsporidia. Thrombocytopenia occurred in 2 of the 6 patients randomized to receive fumagillin. No data are available on use of fumagillin or TNP-470 in HIV-infected children, and neither drug is available for systemic use in the United States. Despite the lack of experience using these agents in children, fumagillin and TNP-470 (where available), in addition to ART, are recommended based on demonstration of efficacy in adults. Consultation with an expert is recommended.

Keratoconjunctivitis caused by microsporidia in HIV-infected adults responds to topical therapy with investigational fumagillin eye drops prepared from Fumidil B® (fumagillin bicyclohexylammonium, a commercial product used to control a microsporidia disease of honeybees) in saline to achieve a concentration of 70 µg/mL of fumagillin.[24-27] Topical therapy with investigational fumagillin eye drops, in addition to ART, is recommended for HIV-infected children with keratoconjunctivitis caused by microsporidia. The addition of oral albendazole to topical fumagillin can be considered for keratoconjunctivitis due to microsporidia other than infections with *Enterocytozoon* or *V. corneae*, because microsporidia may persist systemically despite clearance from the eye with topical therapy alone.[28,29] Children with suspected keratoconjunctivitis that is unresponsive to antibacterial or antiviral therapy should be referred to a pediatric ophthalmologist for evaluation for possible microsporidiosis.

Other agents, including nitazoxanide, atovaquone, metronidazole, and fluoroquinolones, have been reported to reduce diarrhea associated with microsporidia infection. However, metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis. The role of alternative agents or the use of combination regimens for initial therapy is unknown; albendazole remains the preferred therapy for GI tract and disseminated infection caused by microsporidia other than *E. bieneusi* and *V. corneae*.[21,30,31]

### *Monitoring and Adverse Events (Including IRIS)*

Patients with diarrhea should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In severely ill patients, total parenteral nutrition may be indicated.

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

There has been one report of immune reconstitution inflammatory syndrome (IRIS) following initiation of ART in a patient with *E. bieneusi* infection,[32] but IRIS has not been described in association with treatment for non-*E. bieneusi* microsporidiosis. Concern for IRIS should not delay institution of ART in the presence of microsporidia infection.

### *Managing Treatment Failure*

The only feasible approaches to managing treatment failure are supportive treatment and optimization of ART to achieve full virologic suppression. The roles of alternative and combination therapy are unknown.

## Secondary Prevention

No pharmacologic interventions are known to be effective in preventing recurrence of microsporidiosis. However, the use of ART alone in patients with microsporidiosis has resulted in clearance of infection and symptoms,[15] suggesting that improvements in the immune system after successful ART are critical to recovery and may prevent recurrence. Continued albendazole therapy after treatment for an acute episode of GI or disseminated infection caused by microsporidia other than *E. bieneusi* and *V. corneae* may be considered in those with severe immunosuppression (CDC immunologic category 3) until immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2).

For keratoconjunctivitis, discontinuation of fumagillin and albendazole treatment may be considered after resolution of infection in patients and immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2). Therapy should be continued indefinitely if severe immunosuppression (CDC immunologic category 3) persists because recurrence or relapse may follow treatment discontinuation.

### *Discontinuing Secondary Prophylaxis*

Discontinuation of secondary prophylaxis can be considered when immune recovery is observed (longer than 6 months at CDC immunologic category 1 or 2).

## Recommendations

### *Treatment*

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

- Effective ART is the primary initial treatment for microsporidiosis in HIV-infected children **(strong, very low)**.

  An observational study of four adults with documented *E. bieneusi* infection followed stool samples and duodenal biopsy pre-ART, then 1–3 and 6 months post-ART.[15] Results demonstrated that if the patient responded to ART, symptoms related to microsporidiosis improved within 1 month and evidence of eradication of the organism occurred at 6 months. Unfortunately, there are no comparable data for children.

- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided **(expert opinion)**.

  There are no studies that address this specific management issue in microsporidiosis. However, recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.

- Albendazole, in addition to ART, is also recommended for initial therapy of microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(strong, low)**.

  Albendazole has activity against many species of microsporidia but it is not effective against *E. bieneusi* or *V. corneae*. Small observational cohort studies in adults have demonstrated improvement in symptoms and resolution of diarrhea as well as clearance of the organism in some patients following albendazole treatment.[17,18] A large randomized, open-label study in immunocompetent children in Costa Rica demonstrated clinical improvement in 95% of children receiving albendazole within 48 hours of initiation of therapy compared with only 30% who received supportive care only.[19] Case reports suggest that albendazole therapy is not effective in cases of infection with *E. bieneusi* and *V. corneae*.[20] In these cases, systemic fumagillin therapy, where available, is recommended.

- Systemic fumagillin (where available) in addition to ART is recommended for microsporidiosis caused by *E.bieneusi* and *V. corneae* **(strong, moderate)**.

  In a placebo-controlled study of immunocompromised adults (10 of 12 of whom were HIV-infected adults) with *E. bieneusi* microsporidiosis, fumagillin (20 mg/dose orally 3 times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidia spores, which was not observed in placebo recipients.[23] Placebo recipients received fumagillin at the conclusion of the trial and all 6 demonstrated clearance of microsporidia.

- Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia **(strong, very low)**.

  Improvements have been demonstrated in a small number of reported cases of topical fumagillin treatment of microsporidial keratoconjunctivitis. Treatment with this agent is complicated by lack of a licensed preparation in the United States.[24-27]

- Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(expert opinion)**.

  The addition of oral albendazole to topical fumagillin can be considered for keratoconjunctivitis caused by microsporidia other than *E. bieneusi* or *V. corneae* because microsporidia may persist systemically despite clearance from the eye with topical therapy alone.[28,29]

## *Secondary Prevention*

**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 CDC immunologic category 1 or 2) and clinical signs and symptoms of infection are resolved **(weak, very low)**.

Recurrence of microsporidiosis has been documented following discontinuation of treatment in severely immunosuppressed patients.[24] However, discontinuation of therapy following immune restoration resulting from initiation of ART was successful in a small number of patients.[15]

## Dosing Recommendations for Preventing and Treating Microsporidiosis

| Preventive Regimen | | | |
|---|---|---|---|
| **Indication** | **First Choice** | **Alternative** | **Comments/Special Issues** |
| Primary Prophylaxis | N/A | N/A | Not recommended |
| Secondary Prophylaxis | Disseminated, Non-Ocular Infection or GI Infection Caused by Microsporidia Other Than *E. bieneusi* or *V. corneae*:<br>• Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily<br>Ocular Infection:<br>• Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) plus, for infection attributed to microsporidia other than *E. bieneusi* or *V. corneae*, albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection | N/A | Criteria for Discontinuing Secondary Prophylaxis:<br>• After initiation of ART, resolution of signs and symptoms and sustained immune reconstitution (more than 6 months at CDC immunologic category 1 or 2) |
| Treatment | Effective ART Therapy:<br>• Immune reconstitution may lead to microbiologic and clinical response.<br>For Disseminated (Not Ocular) and Intestinal Infection Attributed to Microsporidia Other Than *E. bieneusi* or *V. corneae*:<br>• Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily (in addition to ART)<br>*Treatment Duration:*<br>• Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms<br>For *E. bieneusi* or *V. corneae* Infections:<br>• Fumagillin (where available) adult dose 20 mg by mouth 3 times daily, *or*<br>• TNP-470 (a synthetic analogue of fumagillin; where available) recommended for treatment of infections caused by *E. bieneusi* in HIV-infected adults (in addition to ART)<br>For Ocular Infection:<br>• Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) plus, for microsporidial infection other than *E. bieneusi* and *V. corneae*, albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection (in addition to ART)<br>*Treatment Duration:*<br>• Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms. | N/A | • Supportive care (e.g., hydration, correction of electrolyte abnormalities, nutritional support)<br>• Fumagillin for systemic use is unavailable in the United States and data on dosing in children are unavailable. Consultation with an expert is recommended. |

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; GI = gastrointestinal; QID = 4 times a day

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# Mpox

**Updated:** September 14, 2023
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On July 23, 2022, the World Health Organization declared mpox a global health emergency. Mpox virus is a member of the Poxviridae family (genus Orthopoxvirus). The first person identified in the current outbreak in the United States was confirmed in May 2022, and mpox was declared a public state of emergency in the United States on August 4, 2022. This serious emerging outbreak is currently more common among gay, bisexual, and other men who have sex with men than the general population. Sporadic cases have been reported in children and pregnant people. To date, there are no definitive data that mpox differentially infects people with or without HIV. However, reports do suggest mpox could be an opportunistic infection in people with HIV. People with advanced HIV or who are not virologically suppressed with antiretroviral therapy can be at increased risk of severe disease related to mpox virus infection.

Pre- and post-exposure prophylaxis and antiviral treatments are available for people who are at increased risk of severe disease and are exposed to mpox or diagnosed with mpox virus infection. The first-line antiviral treatment tecovirimat (TPOXX) is effective in animal models in treating disease caused by orthopoxviruses and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of smallpox in adults and children. Tecovirimat is available through the Centers for Disease Control and Prevention (CDC) for compassionate use for mpox infection through an investigational drug protocol. TPOXX can affect metabolism via cytochrome P450 pathways and have some notable drug–drug interactions. Individuals on antiretrovirals and other medications may require drug dosing adjustments with concomitant TPOXX administration. More information can be found in the Adult and Adolescent Antiretroviral Guidelines, Table 24b: Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs. An effective, FDA-approved live attenuated, non-replicating smallpox and mpox vaccine (JYNNEOS) is currently available for pre- and post-exposure prophylaxis in limited settings. Pre- and post-exposure prophylaxis can be considered for people at increased risk of mpox infection, including gay, bisexual, and other men who have sex with men and individuals with close contact exposure to a confirmed mpox case. Vaccination with JYNNEOS is considered safe for people with HIV. CDC has released clinical guidance for prevention and treatment of mpox in immunocompromised people, including people with HIV.

Currently, the best source of information about management of mpox can be found on CDC's Clinical Guidance webpage, which includes clinical considerations for mpox in children and adolescents, as well as considerations for breastfeeding a child who has mpox and for neonates born to individuals with suspected or confirmed mpox. Additional resources can be found on IDSA's Mpox webpage.

# *Mycobacterium avium* Complex Disease (Last updated January 8, 2019; last reviewed January 8, 2019)

| Panel's Recommendations |
|---|
| I. Is prophylaxis for *Mycobacterium avium* complex (MAC), with either clarithromycin, azithromycin, or rifabutin, indicated in children with HIV infection who have advanced immunosuppression to prevent MAC infection? |
| • Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV infection who have advanced immunosuppression (strong, low)<br>• Children aged <1 year: <750 cells/mm$^3$<br>• Children aged 1 to <2 years: <500 cells/mm$^3$<br>• Children aged 2 to <6 years: <75 cells/mm$^3$<br>• Children aged ≥6 years: <50 cells/mm$^3$ |
| • 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. 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?** |
| • 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/mm$^3$ for children aged ≥6 years [strong, high]; and >200 cells/mm$^3$ for children aged 2 to <6 years [strong, moderate]). |
| III. In children with HIV infection and MAC disease, is testing MAC isolates for susceptibility indicated to guide management? |
| • Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (strong, very low). |
| **IV. 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?** |
| • 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. In children with HIV infection and MAC disease, does the use of clarithromycin (as compared to azithromycin) improve clearance of bacteremia? |
| • 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. 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? |
| • 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. In patients with HIV infection and MAC infection who are antiretroviral naive, what is the optimal timing to start ART to prevent IRIS?** |
| • 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. |

X. 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/mm$^3$ for children aged ≥ 6 years [**strong, low**] and >200 cells/mm$^3$ 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

## Epidemiology

*Mycobacterium avium* complex (MAC) refers to multiple related species of nontuberculous mycobacteria (NTM) (e.g., *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium paratuberculosis*) that are widely distributed in the environment. Recent surveillance data have shown an increasing rate of MAC infection in some regions within the United States.[1] Comprehensive guidelines on the diagnosis, prevention, and treatment of nontuberculous mycobacterial diseases were published in 2007.[2] These guidelines highlight the tremendous advances in mycobacteriology laboratory methods that have expanded the number of known NTM species from 50 in 1997 to 125 in 2006. In the United States, NTM infections outnumber *Mycobacterium tuberculosis* infections and have become an important cause of pulmonary morbidity in adults.[3] In children, it appears that the overall prevalence of NTM is increasing over time.[4,5] Disseminated NTM is rare in children who are immunocompetent.

Before the advent of antiretroviral therapy (ART), MAC was second only to *Pneumocystis jirovecii* pneumonia among opportunistic infections (OIs) in children with HIV infection in the United States. With the availability of ART, the incidence of MAC has greatly decreased from 1.3 to 1.8 episodes per 100 person-years in the pre-ART era to 0.14 to 0.2 episodes per 100 person-years in the ART era.[6,7] MAC is ubiquitous in the environment and presumably is acquired by routine exposures through inhalation, ingestion, or inoculation.[8] A population-based study of adults and children in Florida associated soil exposure, black race, and birth outside the United States with MAC infection.[9] Respiratory and gastrointestinal (GI) colonization can act as portals from which infection can disseminate.[10]

MAC can appear as isolated lymphadenitis in children with and without HIV. Disseminated infection with MAC in pediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4 T lymphocyte (CD4) cell count but can occur at higher CD4 counts in younger children with HIV than in older children or adults with HIV. MAC is a recognized complication of advanced immunologic deterioration among children with HIV infection.[8,11,12]

## Clinical Manifestations

Respiratory symptoms are uncommon in children with HIV infection who have disseminated MAC, and isolated pulmonary disease is rare. Early symptoms can be minimal and may precede mycobacteremia by several weeks. Symptoms commonly associated with disseminated MAC infection in children include persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue, persistent diarrhea, and persistent or recurrent abdominal pain. Mesenteric adenitis may mimic acute appendicitis. GI symptoms can occur alone or in combination with systemic findings. Lymphadenopathy, hepatomegaly, and splenomegaly may occur. Laboratory abnormalities include anemia, leukopenia, and thrombocytopenia. Although children with disseminated MAC usually have normal serum chemistries, some children may have elevated alkaline phosphatase or lactate dehydrogenase levels. However, even in the absence of disseminated MAC, these signs and symptoms are relatively common in children with HIV and advanced immunosuppression.

## Diagnosis

Procedures used to diagnose MAC in children with HIV infection are the same as those used for adults with HIV infection.[13] MAC is definitively diagnosed by isolation of the organism from blood or from biopsy specimens from normally sterile sites (e.g., bone marrow, lymph node). Blood cultures are a sensitive and minimally invasive technique for the diagnosis of disseminated MAC as >90% of individuals in whom MAC is diagnosed have positive blood cultures.[2,14] Multiple mycobacterial blood cultures over time may be required to yield a positive result. The volume of blood sent for culture also influences yield, with increased volume leading to increased yield. Use of a radiometric broth medium or lysis-centrifugation culture technique can enhance recovery of organisms from blood. Nucleic acid probes that can identify MAC isolates once growth is detected are also commercially available. These organisms can also be rapidly identified by their mycolic acid patterns from the same samples by high-performance liquid chromatography, though this diagnostic technique may only be available at high volume laboratories.

Histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection in a patient with typical signs and symptoms, but culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis*, to determine which nontuberculous mycobacterium is causing infection, and to perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is most useful as clinical response is correlated with macrolides susceptibility.[2] As with tuberculosis testing, multiplex polymerase chain reaction testing platforms have been developed for rapid identification and drug susceptibility testing, but these technologies are currently only available in research laboratories.[15-17]

Although detection of MAC in stool or the respiratory tract may precede disseminated disease, no data demonstrate a correlation between initiation of prophylaxis in patients with detectable organisms at these sites and reduced risk of developing disseminated MAC.

## Prevention Recommendations

### *Preventing Exposure*

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance.[1] Person-to-person transmission is not believed to be common.

### *Preventing First Episode of Disease*

The most effective way to prevent disseminated MAC in children with HIV infection is to preserve immune function through use of effective ART. Children with HIV infection who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the CD4 count thresholds for children. Before prophylaxis is initiated in at-risk children, disseminated MAC disease must be ruled out, which includes obtaining a blood culture for MAC.[2]

## Treatment Recommendations

### *Treating Disease*

Disseminated MAC infection should be treated in consultation with a pediatric infectious disease specialist who has expertise in pediatric HIV infection. Combination therapy of MAC (with at least 2 drugs, typically a macrolide and ethambutol) and improved immunologic status with ART is important for controlling disseminated MAC disease. Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.[18] Clarithromycin levels can be increased by protease inhibitors (PI) and decreased by efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin is not metabolized by the cytochrome P450 (CYP450) system; therefore, it can be used without concern for significant drug interactions with PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The addition of rifabutin as a third drug to combination therapy of MAC is controversial. Rifabutin increases CYP450 activity that leads to increased clearance of other drugs (e.g., PIs, NNRTIs), which should prompt careful review of drug interactions if such drugs are administered concomitantly and may also warrant more intensive toxicity monitoring.[19] No pediatric formulation of rifabutin exists, but the drug can be administered mixed with foods such as applesauce. Rifabutin can also be compounded in a liquid formulation by a pharmacist. Limited safety data are available from a study in 22 children with HIV infection (median age: 9 years) who received rifabutin in combination with 2 or more other antimycobacterial drugs for treatment of MAC for 1 to 183 weeks; doses ranged from rifabutin 4 mg/kg to rifabutin 18.5 mg/kg, and reported adverse effects were similar to those reported in adults.[20] The most commonly reported dose in children has been rifabutin 5 mg/kg. Therapy is typically prolonged and depends upon response and immune reconstitution.

In the United States, treatment with ART has become the standard practice for all children with HIV. The optimal time to start ART in children with disseminated MAC is unknown; many experts treat MAC with antimycobacterial therapy for 2 weeks before starting ART to minimize immune reconstitution inflammatory syndrome (IRIS). For children already receiving ART, their ART regimen should be continued and optimized with careful attention to potential drug interactions between the ARV and antimycobacterial drugs.

### *Monitoring and Adverse Events, Including IRIS*

Clinically, most patients improve substantially during the first 4 to 6 weeks of therapy. A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiation of antimycobacterial therapy in patients who fail to respond clinically to their initial treatment regimen. Some experts would consider a repeat blood culture for all patients with an initial positive culture, regardless of clinical response to therapy. Improvement in fever can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response may be delayed, and elimination of the organism from the blood may require up to 12 weeks of effective therapy.

Adverse effects from clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels or hypersensitivity reactions. The major toxicity associated with ethambutol is optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, which usually is reversible and rare at doses of 15 to 25 mg/kg in children with normal renal function. The risks and benefits of using ethambutol in very young children whose visual acuity cannot be monitored must be carefully considered.[21,22]

Patients receiving clarithromycin plus rifabutin should be observed for the rifabutin-related development of leukopenia, uveitis, polyarthralgias, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some children with HIV infection receiving rifabutin as part of a multidrug regimen for MAC.[20]

When deciding whether to begin immediate ART in children with very low CD4 counts, the urgent need for rapid immunologic improvement must be considered alongside the possibility of IRIS due to MAC. IRIS in patients receiving MAC therapy and ART has been reported in adults and children with HIV infection.[23-26] New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal lymphadenitis (cervical, thoracic, or abdominal), associated with preexisting—but relatively asymptomatic—MAC infection have occurred after the start of ART (unmasking IRIS). In addition, paradoxical worsening of systemic or local symptoms of MAC may occur as the immune system is rapidly reconstituted. Mycobacteremia is typically absent.

### *Managing Treatment Failure*

MAC 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. Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone. Data from treating MAC in patients without HIV suggest the use of injectable agents such as amikacin or streptomycin may be additional considerations.[2,3]

### *Preventing Recurrence*

Children with a history of disseminated MAC should be given prophylaxis to prevent recurrence until their immune systems are reconstituted. Prophylaxis in this setting means continuation of multidrug therapy because use of a single agent (clarithromycin or azithromycin) for secondary prophylaxis carries a high risk of inducing drug-resistant MAC infection.

### *Discontinuing Secondary Prophylaxis*

On the basis of immune reconstitution data in adults[21,27] and data in children discontinuing primary prophylaxis, some experts recommend discontinuing secondary prophylaxis in children with HIV infection who are aged ≥2 years and have completed ≥12 months of treatment for MAC, remain asymptomatic for MAC, and are receiving stable ART (i.e., ART not requiring change for viral or immune failure) and who have sustained (≥ 6 months) CD4 count recovery well above the age-specific targets for initiation of primary prophylaxis.

## Primary Prevention

**I. Is prophylaxis for MAC with either clarithromycin, azithromycin, or rifabutin, alone, indicated in children with HIV infection who have advanced immunosuppression?**

- Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV infection who have advanced immunosuppression (**strong, low**)
  - Children aged <1 year: <750 cells/mm$^3$
  - Children aged 1 to <2 years: <500 cells/mm$^3$
  - Children aged 2 to <6 years: <75 cells/mm$^3$
  - Children aged ≥6 years: <50 cells/mm$^3$

  Based on randomized controlled trials, clarithromycin and azithromycin are the preferred prophylactic agents for adults. While there are no randomized controlled trials in children, either agent is recommended for prophylaxis in children (**strong, low**); oral suspensions of both agents are commercially available in the United States. Combination therapy for prophylaxis generally should be avoided in children because it is not cost effective and increases the risk of adverse events (**strong, low**).

- For children who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use (**weak, very low**).

**II. 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?**

- 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/mm$^3$ for children aged

≥ 6 years [**strong, high**]; and >200 cells/mm$^3$ for children aged 2 to <6 years [**strong, moderate**]).

On the basis of both randomized controlled trials and observational data, primary prophylaxis for MAC can be safely discontinued in adults with HIV infection who respond to ART with an increase in CD4 count.[28,29] In a prospective study that evaluated the incidence of OIs after discontinuation of OI prophylaxis in 63 children with HIV infection with CD4 percentages ≥20% for those aged >6 years and ≥25% for those aged 2 to 6 years, no MAC events were observed during ≥2 years of follow up.[30] No specific recommendations exist for discontinuing MAC prophylaxis in children with HIV infection who are aged <2 years.[30]

## Treatment

**III. In children with HIV infection and MAC disease, is testing MAC isolates for susceptibility indicated to guide management?**

- Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (**strong, very low**).

Retrospective cohort studies have shown macrolide resistance in initial sterile site isolates of MAC from patients with HIV infection.[31] Very small randomized control trials in adults have shown that only macrolide resistance correlates with clinical outcome, and therefore testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended.[32,33]

**IV. In children with HIV infection and MAC disease, does combination therapy with either clarithromycin or azithromycin plus ethambutol, as opposed to monotherapy, prevent or delay the emergence of resistance?**

- Combination therapy with a minimum of 2 drugs (e.g., either 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.

There is a lack of pediatric literature to guide the clinical management of children with HIV infection with disseminated MAC. Small retrospective studies confirm the incidence of MAC in severely immunosuppressed children.[34,35] Studies in adults showed that combination therapy of MAC with a minimum of 2 drugs prevented or delayed emergence of resistance.[33,36-40] In a study evaluating combination MAC therapy, there was no difference in relapse rates between treatment with the combination of clarithromycin and ethambutol or with both drugs plus rifabutin, suggesting that rifabutin did not provide any additional benefit.[39]

**V. In children with HIV infection and MAC disease, does the use of clarithromycin (as compared to azithromycin) improve clearance of bacteremia?**

- There are insufficient data to recommend the use of clarithromycin over azithromycin. On the basis of a small randomized controlled trial in adults, which showed that the median time to clearance was shorter for clarithromycin than for azithromycin (4.4 versus >16 weeks) and that the organism was eliminated from the bloodstream in 86% of the patients in the clarithromycin group and in only 38% of those in the azithromycin group, some experts use clarithromycin as the preferred first agent. Azithromycin is reserved for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern (**strong, low**).

**VI. 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?**

- Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial (**weak, very low**).

Pediatric studies are lacking, but one randomized controlled open label study in adults compared clarithromycin plus ethambutol to clarithromycin plus rifabutin versus clarithromycin + ethambutol + rifabutin. While microbiologic response was similar, the 3-drug arm had improved mortality, as well as less relapse of infection.[39] There were no noted differences in the development of resistance in those who relapsed. On the basis of these studies, some experts would add rifabutin as a third drug to the clarithromycin plus ethambutol regimen, particularly in the absence of ART and in the presence of high mycobacterial counts. However, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy (**strong, very low**).[19]

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 PIs and NNRTIs, and the potential for increased toxicity associated with concomitant administration of drugs. Guidelines and recommendations exist for dose adjustments necessary in adults treated with rifabutin and PIs, but the absence of data in children precludes extrapolating these guidelines and recommendations to children with HIV undergoing treatment for disseminated MAC.

**VII. In patients with HIV with MAC infection who are antiretroviral naive, what is the optimal timing to start ART to prevent IRIS?**

- In patients with disseminated MAC disease who have not been treated previously with or are not receiving effective ART, initiation of 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. However, ART should be started as soon as possible after the first 2 weeks of initiating antimycobacterial therapy to reduce the risk of developing additional AIDS-defining OIs, and to facilitate immune reconstitution and further improve the response to antimycobacterial therapy (**weak, very low**). Children with moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) or, if unresponsive to NSAIDS, a short course (such as 4 weeks) of systemic corticosteroid therapy while continuing to receive ART.

**VIII. In patients with HIV and MAC infection with treatment failure (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?**

- 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.

## Secondary Prevention

**IX. In children with HIV 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, very low**). Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.

There are no pediatric data regarding secondary prophylaxis for MAC infection; however, low quality evidence from a randomized clinical trial in adults showed no difference in relapse rates in participants receiving the combination of clarithromycin, ethambutol, and rifabutin and in those receiving the combination of clarithromycin and ethambutol, but the 3-drug regimen showed a reduction in mortality.[39]

There remain concerns regarding toxicity and drug interactions with rifabutin. There are no data that look at azithromycin plus ethambutol for secondary prophylaxis. Prophylaxis in this setting means continuation of multidrug therapy, because use of a single agent (clarithromycin or azithromycin) for secondary prophylaxis carries a high risk of inducing drug-resistant MAC infection.

**X. In children with HIV 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 who meet **all** 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/mm$^3$ for children aged ≥6 years [**strong, low**], and >200 cells/mm$^3$ for children aged 2 to <6 years [**weak, very low**]).

There are no randomized clinical trials in children on discontinuation of secondary prophylaxis. On the basis of immune reconstitution data in adults[41-44] and data in children discontinuing primary prophylaxis[30], some experts recommend discontinuation of secondary prophylaxis in children with HIV aged ≥2 years who have completed ≥12 months of treatment for MAC, remain asymptomatic for MAC, and are receiving stable ART (i.e., ART not requiring change for viral or immune failure) and who have sustained (≥ 6 months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (as in adults, >100 cells/mm$^3$ for children aged ≥6 years [strong, low] and >200 cells/mm$^3$ for children aged 2 to <6 years [**weak, very low**]). Multidrug secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

**Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex (MAC)** (page 1 of 2)

| Preventive Regimen | | | |
|---|---|---|---|
| Indication | First Choice | Alternative | **Comments/Special Issues** |
| Primary Prophylaxis | • Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, *or*<br>• Azithromycin 20 mg/kg body weight (maximum 1200 mg) orally once weekly | • Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily<br>• Children aged >5 years: rifabutin 300 mg orally once daily with food | Primary Prophylaxis Indicated for Children:<br>• Aged <1 year: CD4 count <750 cells/mm$^3$;<br>• Aged 1 to <2 years: CD4 count <500 cells/mm$^3$;<br>• Aged 2 to <6 years: CD4 count <75 cells/mm$^3$;<br>• Aged ≥6 years: CD4 count <50 cells/mm$^3$<br>Criteria for Discontinuing Primary Prophylaxis:<br>• Do not discontinue in children aged <2 years.<br>• After ≥6 months of ART, *and*:<br>  • Aged 2 to <6 years: CD4 count >200 cells/mm$^3$ for >3 consecutive months<br>  • Aged ≥6 years: CD4 count >100 cells/mm$^3$ for >3 consecutive months<br>Criteria for Restarting Primary Prophylaxis:<br>• Aged 2 to <6 years: CD4 count <200 cells/mm$^3$<br>• Aged ≥6 years: CD4 count <100 cells/mm$^3$ |

**Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex (MAC)** (page 2 of 2)

| Preventive Regimen | | | |
|---|---|---|---|
| Indication | First Choice | Alternative | **Comments/Special Issues** |
| **Secondary Prophylaxis** (Chronic Suppressive Therapy) | • Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, plus<br>• Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food<br>• Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food | • Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily, plus<br>• Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food<br>• Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food | Secondary Prophylaxis Indicated:<br>• Prior disease<br>Criteria for Discontinuing Secondary Prophylaxis<br>*Fulfillment of All of the Following Criteria:*<br>• Completed ≥6 months of ART<br>• Completed ≥12 months MAC therapy<br>• Asymptomatic for signs and symptoms of MAC<br>• Aged 2 to <6 years: CD4 count >200 cells/$mm^3$ for ≥6 consecutive months<br>• Aged ≥6 years: CD4 count >100 cells/$mm^3$ for ≥6 consecutive months<br>Criteria for Restarting Secondary Prophylaxis:<br>• Aged 2 to <6 years: CD4 count <200 cells/$mm^3$<br>• Aged ≥6 years: CD4 count <100 cells/$mm^3$ |
| **Treatment** | Initial Treatment (≥2 Drugs):<br>• Clarithromycin 7.5–15 mg/kg body weight (maximum 500 mg/dose) orally twice daily plus ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) orally once daily followed by chronic suppressive therapy<br>For Severe Disease, Add:<br>• Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) orally once daily | If Intolerant to Clarithromycin:<br>• Azithromycin 10–12 mg/kg body weight (maximum 500 mg/day) orally once daily<br>If Rifabutin Cannot Be Administered and a Third Drug is Needed in Addition to a Macrolide and Ethambutol, or if a Fourth Drug is Needed in Addition to Rifabutin for Patients with More Severe Symptoms or Disseminated Disease:<br>• Ciprofloxacin 10–15 mg/kg orally twice daily (maximum 1.5 g/day), or<br>• Levofloxacin 500 mg orally once daily, or<br>• Amikacin 15–30 mg/kg body weight IV in 1 or 2 divided doses (maximum 1.5 g/day) | Combination therapy with a minimum of 2 drugs is recommended for ≥12 months.<br>Clofazimine is associated with increased mortality in adults with HIV infection and should not be used.<br>Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination.<br>Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are not labeled for use in children aged <18 years because of concerns regarding potential effects on cartilage; use in children aged <18 years requires an assessment of potential risks and benefits.<br>Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. |

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* complex; IV = intravenous

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# *Mycobacterium tuberculosis*

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## Panel's Recommendations

I. 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)?

- 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. Among children <15 years old with HIV, does a negative TST or IGRA reliably exclude TB infection or disease?

- 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. Among children <15 years old with HIV, does LTBI treatment result in fewer cases of TB disease, compared to no treatment?

- 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. 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?

- 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. 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?

- 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**).

- After exposure to TB caused by organisms with other drug resistance patterns (e.g., multidrug-resistant [MDR]), expert consultation should be obtained to determine optimal LTBI treatment regimens. DST results for the TB index patient are important considerations in the management of children exposed to drug-resistant TB (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 or Weak*

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

## Definitions

### *Latent Tuberculosis Infection*

Latent tuberculosis (TB) infection (LTBI), as referred to by the Centers for Disease Control and Prevention (CDC), or TB infection (TBI), as indicated by the American Academy of Pediatrics' Red Book, is defined as a state of persistent immune response to stimulation by antigens of bacteria in the *Mycobacterium tuberculosis* complex (MTBC; e.g., *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*) without any clinical, radiographic, or microbiologic evidence of disease. People with LTBI/TBI are not contagious and have no signs or symptoms of tuberculosis (TB) disease. Nonetheless, they are at increased risk for developing TB disease and becoming contagious; diagnosing and treating LTBI/TBI can help prevent progression to TB disease.

### *Tuberculosis Disease (Also Called "Active Disease")*

TB disease occurs when a person with MTBC has clinical signs and/or symptoms, radiographic evidence, or viable mycobacteria recovered from a clinical specimen. Disease can be pulmonary, extrapulmonary, or both.

**Note:** The terms "active" and "latent" are not universally accepted, because they imply a clear distinction between two states when there is instead a continuum from infection to disease, particularly in children who often have paucibacillary disease.

## Introduction

### *Epidemiology*

Information on the epidemiology of TB in the United States is available from the CDC.[1,2] Of the 8,300 TB cases provisionally reported in the United States during 2022, 362 (4.3%) occurred in children aged <15 years.[1] Among TB cases with known HIV status reported in the United States between 2008 and 2010, HIV coinfection was reported in 1.1% of children and adolescents <18 years old.[3] The actual rate of HIV coinfection in children and adolescents with TB in the United States is unknown during this period because of the low rate of HIV testing documented in national surveillance for this population—approximately 55% of TB cases did not have an HIV result reported to the National TB Surveillance System despite recommendations for routine HIV testing in all individuals with confirmed or suspected TB.

Numerous studies have documented an increased risk of TB in children and adults with HIV.[4-6] A decreasing or low CD4 T lymphocyte (CD4) cell count is not necessary for an increased risk of TB in children with HIV. However, decreasing CD4 cell counts reflect diminishing immunity, which further increases the risk for TB disease. Multiple studies conducted in resource-limited settings have demonstrated that among children with HIV, those with TB disease tend to have lower CD4 cell counts and percentages than those without TB disease.[7-9] In addition, while rare, congenital TB might be more common among children born to mothers with TB/HIV coinfection,[10,11] especially when those children have also perinatally acquired HIV.[11]

Most often, children with TB acquired the infection from an adult in their immediate environment; frequently, TB in children, especially young children, represents progression of a primary infection rather than the reactivation of an infection acquired in the past.[12] Diagnosis and treatment of the source cases and evaluation of household contacts exposed to TB disease are important measures to identify individuals at high risk of infection, diagnose LTBI and TB disease promptly, and prevent more transmission.[13-15] All confirmed and suspected cases of TB disease should be reported to state and local health departments.[15]

In the United States, disease caused by *Mycobacterium bovis* (*M. bovis*) is thought to be far less common than disease caused by *M. tuberculosis*, but pediatric *M. bovis* cases have been reported, and children might have an increased relative prevalence of *M. bovis* disease.[16,17] Of the 165 cases of TB known to be caused by *M. bovis* in the United States between 1995 and 2005, 12 (7.3%) were in children aged 0 to 4 years, and 19 (11.5%) were in children aged 5 to 14 years.[16] Several reports suggest that *M. bovis* is primarily transmitted via ingestion of unpasteurized dairy products[16,18]; however, human-to-human airborne transmission has been reported.[19-21] *M. bovis* is considered intrinsically resistant to pyrazinamide, a characteristic that could influence treatment decisions.[22,23]

The emergence and effective transmission of drug-resistant TB is a major obstacle to global TB control.[24-26] In the United States, comprehensive public health measures have successfully reduced the rates of drug-resistant TB; among reported cases of TB, the proportion of primary multidrug-resistant (MDR)-TB cases, defined as cases resistant to at least isoniazid and rifampin, declined from 2.5% in 1993 to less than 1% since 1996.[2] Between 2008 and 2010, resistance to isoniazid was found for 7.8% of culture-confirmed TB cases occurring in children and adolescents (aged <18 years) and MDR-TB was found in 4% of non-U.S.–born and 1% of U.S.-born children in the United States who had culture-confirmed TB and drug-susceptibility testing (DST) results reported to the CDC.[3]

Extensively drug-resistant TB (XDR-TB) was traditionally defined as resistance to isoniazid and rifampin (i.e., MDR-TB), with additional resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin). In 2021, the World Health Organization (WHO) updated the XDR-TB definition; according to WHO, XDR is TB caused by MDR or rifampin-resistant (RR) *M. tuberculosis* strains that are also resistant to any fluoroquinolone and at least one additional Group A drug (i.e., bedaquiline or linezolid); CDC has also updated the United States definition of XDR-TB.[27,28] CDC defines XDR as TB caused by *M. tuberculosis* strains that are resistant to isoniazid, rifampin, a fluoroquinolone and a second-line injectable agent (e.g., amikacin, capreomycin, and kanamycin).[28] CDC also considers *M. tuberculosis* strains resistant to isoniazid, rifampin, a fluoroquinolone, bedaquiline, and linezolid to be XDR.[28] XDR-TB has emerged globally as an important new threat.[24,26,29] Of the 49 cases of XDR-TB reported in the United States from 1993 to 2006, one (2%) was in a child aged <15 years.[30]

## *Clinical Manifestations*

After acquiring *M. tuberculosis* complex, children aged <5 years old and children with immune-compromising conditions, such as HIV, are highly susceptible to developing symptomatic TB disease; the first 12 months after primary infection represents the period of greatest risk for progression to TB disease.[6,12,31] Children <5 years old and children with HIV can also develop TB disease after a primary infection of *M. tuberculosis* complex. Generally, the clinical features of TB disease in children with and without HIV are similar, with non-localizing signs such as failure to thrive, cough, and intermittent fever present. Disease progression, however, may be more rapid, and the development of complicated or disseminated disease is more likely in children with HIV.[12,32-34] Regardless of HIV status, children may present with characteristic pulmonary involvement such as hilar and/or mediastinal adenopathy, which may cause airway compression. In addition, children who are immunocompromised, including those with HIV, might have atypical findings such as multi-lobar infiltrates and diffuse interstitial disease.[5,35] Rapidly progressive disease, including meningitis or mycobacterial sepsis, is more likely among very young children or those who are immunocompromised, including in children with HIV.

The following describes the natural history of childhood TB, although children with HIV of all ages are more likely to have disease manifestations similar to those seen in very young children.[12,36,37]

- **Aged <1 year:** Infants are at the highest risk for disease following primary infection with *M. tuberculosis*: as many as 50% of infants under 12 months of age might progress to active TB disease. Infants with TB are at high risk for extrapulmonary and disseminated disease, such as miliary TB, tuberculous meningitis (TBM), and extensive pneumonic infiltration.
- **Aged 1 to 4 years:** Compared to adults, young children have an elevated risk of disseminated forms of disease. However, this risk is lower than in infants under 1 year old. Children <5 years are at the greatest risk of complications resulting from airway compression because of their small, pliable airways and exuberant lymph node responses. Extrathoracic manifestations are also common (see below).
- **Aged 5 to 9 years:** Immunocompetent children in this age group have the lowest risk of progression to TB disease after primary infection. Still, depending on the average age at which primary infection occurs, TB among children in this age group may contribute substantially to the total case load of pediatric TB. Clinical manifestations in this age group vary; some patients present clinically with disease patterns more commonly seen in young children while others present with adult-type pulmonary disease, upper lobe infiltration, cavitation, and sputum production.
- **Aged >10 years:** Adult-type pulmonary disease is more common. Children in this age group are more likely to have positive results from acid-fast bacteria (AFB) sputum smear microscopy and should be considered potential infectious sources.[38]

The reported proportion of children with TB who have extra-thoracic involvement has ranged widely, from approximately 10% to more than 50%, which is likely due to variations in diagnostic capacity and the timing of presentation; disseminated forms appear to be more common in children with HIV.[33,34,36,37,39,40] Extra-thoracic disease manifestations include:

- **Peripheral lymphadenitis (usually cervical):** Features include a matted mass of lymph nodes >2×2 cm.[41] Axillary adenitis ipsilateral to Bacille Calmette-Guerin (BCG) vaccination site is suggestive of BCG adenitis (also see the Immune Reconstitution Inflammatory Syndrome [IRIS] section below).
- **TBM** is most common in children aged <3 years, but can occur at any age, especially in children with HIV. Although the disease manifestations of TBM in immunocompetent and immunocompromised children are often similar, the list of differential diagnoses is greatly expanded in immunocompromised individuals, including children with HIV.[42,43]
- **Osteo-articular disease** can involve any bone or joint, but vertebral involvement with typical TB gibbus formation with or without para-vertebral abscess formation is most common.
- **Cold abscesses** can occur at any site, but often develop in association with bone involvement or in deep muscle groups, such as psoas muscle.

- A great variety of disease manifestations are possible, including hypersensitivity reactions such as erythema nodosum and phlyctenular keratoconjunctivitis.[44]

## Diagnosis

### *Latent TB Infection*

Because children with HIV are at high risk for developing TB disease, screening questions about exposure to TB should occur at each health care visit; testing for LTBI is recommended beginning at ages 3 to 12 months and annually thereafter for those with negative results **(expert opinion).**[23] More frequent LTBI testing may be needed depending on epidemiologic risk factors, travel history, contact with people with suspected or confirmed TB, or clinical symptoms.

LTBI, which is a symptomless condition in which no viable mycobacteria are recovered from clinical specimens, can be diagnosed using the tuberculin skin test (TST) administered by the Mantoux method or by interferon-gamma release assays (IGRAs). Both testing methods depend on T-cell mediated immune activity; therefore, HIV and the degree of immune alteration influence the accuracy of these tests. Neither TST nor IGRA can be used to definitively exclude TB infection or disease, especially in the context of HIV **(strong, moderate).**[23,45,46]

The interpretation of TST or IGRA results must include consideration of an individual patient's epidemiological and medical factors and the circumstances of testing. The QuantiFERON-TB Gold (QFT) and QFT-Plus (Cellestis Limited, Valencia, California) and the T SPOT.TB assay (Oxford Immunotec, Marlborough, Massachusetts) are U.S. Food and Drug Administration (FDA)-approved. According to CDC guidelines, either an IGRA or TST can be used in children 5 years or older and will perform well in children with well-controlled HIV who are sufficiently nourished **(strong, moderate);** in addition, some experts and the AAP Red Book recommend IGRA use in children ≥2 years old.[23,47-50] Nonetheless, current CDC guidance recommends the use of TST in children 2 to 5 years old. An IGRA is preferred for testing BCG-vaccinated patients and for use in settings when the return rate for TST reading is poor **(strong, moderate).**[50] However, studies of IGRA performance in children with HIV and in very young children are limited, and results from these studies have been inconsistent; data on the sensitivity and specificity of IGRAs in children <2 years are not available.[51] CDC and the AAP Red Book preferentially recommend TSTs over IGRAs to test for LTBI in children younger than 2 years **(expert opinion).**[23,26,50,52,53]

When increased sensitivity for diagnosing *M. tuberculosis* infection is sought, both a TST and an IGRA can be done, with a positive result from either test being diagnostic **(expert opinion).** If the tests are performed simultaneously, blood for IGRA testing should be drawn before the TST is administered **(expert opinion).** Younger age, HIV infection, and reduced numbers of CD4 cells increase the rate of indeterminate IGRA results.[54] A recent systematic review and meta-analysis of IGRA use in children also found reduced QuantiFERON-TB Gold sensitivity in young children, which greatly reduced the diagnostic utility of the assay in TB-endemic areas.[53]

### *Interpretation of Tests for M. tuberculosis Infection*

In patients with HIV, ≥5 mm of induration after TST placement is considered a positive test. However, even with this lower cutoff, sensitivity remains poor. It is important that skin tests be administered and interpreted by trained professionals.[23] The CDC offers resources and training materials for administering and interpreting skin tests. The use of control skin antigens to assess cutaneous anergy is not routinely recommended **(expert opinion).** Sensitivity to tuberculin is reduced by severe malnutrition and some viral infections, including measles; the additive effect of HIV in these circumstances has not been determined.[23] As a precaution, skin testing scheduled around the time of live-virus vaccination should be done at the same time as vaccination, or delayed until 4 weeks after, to avoid potentially suppressed sensitivity **(expert opinion).**[23] Test characteristics for IGRAs in the situations described (i.e., severe malnutrition or viral infection in the setting of immunosuppression) have not been determined, but the same scheduling adjustments as for TST are advisable.[50] Two-step skin testing may boost sensitivity in adults, but its utility has not been assessed in children nor in the presence of HIV, and its routine use is not recommended **(expert opinion).** Patients with positive TST or IGRA results should undergo chest radiography and clinical evaluation to exclude TB disease.[23,45,46]

## *TB Disease*

Direct methods for detection of *M. tuberculosis* complex include AFB microscopy, nucleic acid amplification tests (NAATs), and culture. However, the effectiveness of sputum smear microscopy and culture in young children and children with HIV may be limited because these children often have paucibacillary TB disease, which yields sputum with a low bacterial load. In addition, sputum specimens may be difficult to obtain from young children because they cannot expectorate.[23] A positive smear result is suggestive of TB, but it does not differentiate *M. tuberculosis* from other AFB, such as *M. fortiuitum or M. avium*. A positive mycobacterial culture result for MTBC provides a definitive diagnosis of TB disease; culture yield is less than optimal, especially among people with HIV and children. When organisms are successfully grown, culture permits species identification, DST, and genotyping. Because there are many possible causes of similar illness, especially among children with HIV, obtaining a definitive diagnosis by confirming the presence of *M. tuberculosis* complex is helpful in children with HIV.[55] For children who are unable to produce sputum spontaneously, specimens should be collected via sputum induction, nasopharyngeal aspiration or early-morning gastric aspiration. Because the first specimen collected gives the very highest yield, the sample collection should be undertaken carefully. When extrapulmonary involvement is suspected, relevant specimens should be obtained as clinically indicated and sent for histology and culture.[56] Overall diagnostic yield is increased by collecting multiple specimens.[56]

Two FDA-approved commercial NAATs for direct detection of *M. tuberculosis* in sputum samples with positive or negative smear-microscopy results are available in the United States: Amplified Mycobacterium Tuberculosis Direct Test (Gen-Probe) and Xpert MTB/RIF (Xpert, Cepheid), which can also detect rifampin resistance. FDA approval of Xpert MTB/RIF is based on the evaluation of the test's performance on sputum specimens. WHO endorsed use of Xpert MTB/RIF for testing in children, including testing of extrapulmonary specimens, in 2013.[57] NAATs are also recommended for diagnosis of TB in the United States.[58] A meta-analysis of studies that compared the performance of Xpert MTB/RIF to culture on respiratory specimens from children showed sensitivities, compared to culture, of approximately 62% for expectorated or induced sputum and 66% for gastric lavage specimens.[59] A recent meta-analysis showed that the sensitivity of Xpert MTB/RIF relative to culture on extrapulmonary specimens varies by specimen type.[60] Tests for urine lipoarabinomannan (LAM) in children have poor sensitivity and specificity.[61,62]

Drug-resistant TB should be suspected in the following situations[23]:

- History of inadequate previous treatment for TB disease (or exposure to a person who received previous treatment for TB disease)

- Exposure to a person with drug-resistant TB
- Residence in or travel to regions or setting (e.g., an institution such as an orphanage) with high prevalence of drug-resistant TB
- Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks while in a foreign country (i.e., the patient or guardian may not realize that the treatment was for TB)
- Putative source case has positive smears for acid-fast bacilli or cultures after 2 months of an appropriate antituberculosis regimen
- Relapse of TB following a completed course of treatment
- Failure to respond to adequate treatment

Careful inquiry about the drug-susceptibility pattern and treatment history of the likely source case (which should be routinely available for all newly diagnosed adult, culture-confirmed TB cases) is essential to guide clinical management and the choice of treatment regimen in children. TB DST (molecular and phenotypic) should be performed in all cases where *M. tuberculosis* is isolated from a child; obtaining specimen(s) for mycobacterial culture and TB DST is particularly important for those who meet any of the risk criteria for drug resistance or if treatment failure occurs. A service for the molecular detection of drug resistance, provided by CDC through public health microbiology laboratories, provides rapid assessment of drug resistance.[63]

## Prevention Recommendations

Several strategies are necessary for preventing TB-related morbidity among children with HIV, including preventing exposures to infectious TB, minimizing HIV-related immunocompromise with early initiation of antiretroviral therapy (ART),[64-66] and providing prompt diagnoses and treatment for people with LTBI or exposures to infectious TB.[55,67] TB infection control is also critical in health care and congregate settings.[68]

### *Preventing Exposure*

Most childhood infections with MTBC result from exposure to an individual with infectious TB in a child's immediate environment, often within a household. Families should be educated about epidemiologic and social risk factors for TB disease (such as homelessness, congregation in high-risk settings, and birth or residence in a region with a high TB burden), and children with HIV who have been in close contact with people with these risk factors should receive heightened attention. During the peripartum period, women with HIV seem particularly vulnerable to TB, and they should be evaluated for TB disease if they develop any symptoms suggestive of disease, such as unexplained cough, fever, weight loss, or failure to thrive.[69,70]

### *Preventing Disease*

BCG vaccine, which is commonly used to reduce the risk of disseminated TB in high-TB burden countries, should not routinely be administered to infants and children with HIV in the United States **(expert opinion).**[23] BCG is not thought to prevent against pulmonary TB, the most common form of TB in the United States. In the United States, children with HIV should be tested for TB infection beginning during infancy (3–12 months of age) and annually thereafter **(expert opinion).**[23] TST is preferred over IGRA for children aged <2 years **(strong, low).**[23,50]

CDC guidelines stipulate that both TSTs and IGRAs can be used for testing children with HIV for LTBI who are ≥5 years old.[50] In addition, some experts and the AAP Red Book provide recommendations for testing children ≥2 years with IGRAs. TSTs are preferred in children <2 years.[23] IGRAs are preferred for testing BCG-vaccinated people and for use in settings when the return rate for TST reading is low **(strong, moderate).**[50] The value of an annual TB infection testing strategy will depend on the local TB epidemiology, a child's region of birth and travel history, and whether the child has any additional social risk factors for exposure to *M. tuberculosis* (e.g., residence in a congregate setting). After TB disease has been excluded, all children with HIV who have a positive TST or IGRA or who have had close contact with a person with infectious TB (regardless of their TST or IGRA result or previous treatment for TB) should receive preventive therapy **(strong, high).**[46,67,71,72]

In adults and children 2 years and older, including those with HIV, a 12-dose combination regimen of once-weekly isoniazid and rifapentine (3HP) is as safe and effective as 9 months of isoniazid in preventing TB disease.[73-76] Completion rates are high whether given as directly observed therapy (DOT) or self-administered therapy.[77] Therefore, the 3HP regimen can be used for the treatment of LTBI in adults and children ≥2 years old with HIV who are receiving ART, with acceptable drug–drug interactions with rifapentine **(strong, moderate).**[46] The preferred regimens for LTBI from presumed drug-susceptible TB include—

- Twelve doses of weekly isoniazid (for medication dosing recommendations, see the Dosing Recommendations Table) and rifapentine for children and adolescents >2 years old.[46]
- Four months of daily rifampin for children of all ages.
- Three months of daily isoniazid and rifampin for children of all ages.[46]

Alternative regimens include 6 or 9 months of isoniazid for children of all ages.[23] If adherence with treatment cannot be ensured, then DOT by a trained worker can be considered **(expert opinion).**[23,72] There is some evidence to suggest that the risk of isoniazid-related severe liver injury is lower in children with HIV than in adults with HIV.[78] However, it may be necessary to monitor serum transaminases in children with HIV receiving ART and/or with any symptoms or signs suggestive of possible hepatotoxicity. Patients (or their caregivers) should be counseled to discontinue taking the medication and contact their physicians immediately if any symptoms such as excess fatigue, nausea, vomiting, abdominal pain, or jaundice occur.[79] Drug–drug interactions between LTBI medications (particularly rifamycins) and ART should be considered; these interactions might require adjustment of ART.

Dose adjustments with dolutegravir and raltegravir should be considered when administering 4 months of daily rifampin or 3 months of daily rifampin with isoniazid. In children with HIV being treated for TB disease, twice-daily dolutegravir is safe and achieves adequate pharmacokinetic (PK) targets in children >20 kg when co-administered with rifampin **(strong, moderate).**[80] Similarly, raltegravir dosing of 12 mg/kg twice daily is safe and achieves adequate PK targets in children <20 kg when co-administered with rifampin for TB treatment **(expert opinion).**[81]

If isoniazid mono-resistance is known or suspected in the TB source case, daily rifampin for 4 months is recommended, with adjustment of ART as needed **(strong, moderate)** to account for potential drug–drug interactions with rifampin.[23] Children exposed to other drug-resistant TB should receive individualized medical management in consultation with an expert, considering the susceptibility pattern and treatment history of the likely source case.[23,67,82,83]

## Treatment Recommendations

### *Treating Disease*

Empiric therapy for TB disease should be started in infants and children with HIV in whom TB is strongly suspected and continued until treatment is completed or TB disease is excluded **(strong, low).** The use of DOT by a trained health care worker is recommended to maximize adherence and to decrease rates of relapse, treatment failures, and drug resistance **(strong, moderate).**[23,45,84] Principles for treatment of TB are similar for children with and without HIV. However, treating TB in a child with HIV is complicated by ART interactions and overlapping toxicities. The recommended total treatment duration is a minimum of 6 months for children with HIV **(strong, moderate).**[23,45,85]

An overview of dosing recommendations for the prevention and treatment of TB in children with HIV is provided in the Dosing Recommendations Table at the end of this section. In children with HIV, treatment of drug-susceptible TB often involves a four-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol given daily during a 2-month intensive-therapy phase, followed by a 4-month (or more) continuation phase using only isoniazid and rifampin **(strong, moderate).**[23,45,85] 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 and a continuation phase (using isoniazid and rifampin) of 4 months (or more).[23,85]

Ethionamide should be used as an alternative to ethambutol (or an injectable aminoglycoside) for treatment of TBM, because of its superior cerebrospinal fluid penetration **(expert opinion).**[23,85-89] Some experts also routinely add a fluoroquinolone to the initial regimen.[23] For children with extrapulmonary disease involving the bones or joints or central nervous system (CNS), or who have miliary disease, the recommended total duration of treatment is at least 12 months (2-month intensive phase followed by a ≥10-month continuation phase) **(expert opinion).**[23,85,90,91] These recommendations assume that the organism is fully susceptible, that adherence is ensured by DOT, and that a child responds well clinically (and, if laboratory confirmed, microbiologically) to therapy.

### *Co-treatment of TB and HIV*

Concomitant treatment of TB and HIV is complicated by unfavorable PK interactions and overlapping toxicities and should be managed by a specialist with expertise in treating both conditions.

For children already receiving ART, ART should be reviewed to minimize potential toxicities and drug interactions. For children not yet receiving ART, early ART initiation should be planned, preferably beginning within 2 to 8 weeks of starting treatment for TB **(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).** Results from treating TB/HIV coinfection in adults suggest that early initiation of ART after the start of treatment for TB (within 2–8 weeks) may increase the risk of IRIS, but it is associated with a significant reduction in mortality among those with a CD4 count below 50 cells/mm$^3$.[92-95] Results from treating TB/HIV coinfection in children also support early ART initiation.[66,94] Early ART initiation is especially important for children who are severely immunocompromised, and ART initiation within 2 weeks of beginning TB treatment might be advisable, depending on the clinical circumstances **(expert opinion).**[96] The optimal timing of ART initiation in patients with CNS TB has not been established and remains controversial because of the potentially devastating effects of CNS IRIS.[97,98]

## *Drug–Drug Interactions in TB and HIV Co-treatment*

Rifampin is a potent inducer of the CYP3A enzyme system with moderate to significant interactions with nevirapine and protease inhibitors (PIs), respectively, reducing corresponding plasma drug concentrations. Rifabutin, a rifamycin-class semi-synthetic antibiotic related to rifampin, exhibits minimal CYP3A induction and can be used instead of rifampin to reduce drug interactions.[23]

Preliminary results from the ODYSSEY trial in children aged 6 to 18 years receiving TB treatment with rifampin demonstrated that twice-daily DTG dosing was safe and achieved adequate dolutegravir pharmacokinetic targets.[80] Therefore, in children >20 kg, DTG-based ART is the preferred regimen in the context of TB/HIV co-treatment, with 50 mg DTG given twice daily throughout TB treatment. While the FDA has approved twice-daily DTG during TB treatment for children as young as 4 weeks old and ≥3 kg, additional evidence on safety and PK parameters in children <20 kg is needed to inform formal U.S. Department of Health and Human Services recommendations.[99] There are insufficient pharmacokinetic data for the use of bictegravir during TB treatment for children with HIV.

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. Safety and adequate PK targets in children receiving RAL 12 mg/kg twice-daily dosing with concurrent rifampin administration have been demonstrated among children as young as 4 weeks of age.[81,100]Among children <20 kg who are receiving lopinavir (LPV)/ritonavir (LPV/r)-based ART, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (RTV) **(strong, moderate).** Non-inferiority of super-boosted LPV/r PK targets during rifampin treatment was demonstrated in a clinical trial of South African children between 3 to 15 kg receiving rifampin for TB treatment.[101] Alternatively, children <20 kg can receive an efavirenz (EFV)-based regimen **(expert opinion).** If an EFV-based regimen is used, CYP2B6-516 genotype-directed EFV dosing is recommended.

## *Treatment of Drug-Resistant TB*

Children with clinically diagnosed or microbiologically confirmed drug-resistant TB should be managed in consultation with an expert. Therapeutic regimens are individualized based on the resistance pattern of the *M. tuberculosis* isolate and treatment history of the patient and the likely source case, considering the relative activities of each drug, the extent of disease, and any comorbid conditions **(expert opinion).**[23,102]

### Mono-Drug Resistant TB

If the TB strain is resistant only to isoniazid, isoniazid should be discontinued and the patient treated for 6 to 9 months with a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol) **(expert opinion).**[23,85] The addition of a late-generation fluoroquinolone for the duration of treatment is also now suggested.[23,102] Rifampin mono-resistance is thought to be uncommon; therefore, rifampin resistance is considered a reliable marker of MDR-TB (see below). Therefore, if rifampin mono-resistance is detected with a rapid test, it should be regarded as MDR-TB until the susceptibility or resistance to both isoniazid and rifampin is confirmed by phenotypic testing, because the rapid molecular (genotypic) methods for detecting resistance are not as sensitive for isoniazid resistance as they are for rifampin resistance **(expert opinion).**

### Multidrug-Resistant TB

Children with suspected and confirmed MDR-TB should be managed in consultation with an expert **(expert opinion).**[23,102] Treatment should be guided by DST; use of medications to which the *M. tuberculosis* strain is susceptible is associated with better treatment outcomes whereas use of medications to which the *M. tuberculosis* strain is resistant is associated with treatment failure, additional acquired resistance, and unnecessary toxicity.[103-105] In the United States, where DST is widely available, treatment of MDR-TB should be individualized based on results of DST rather than on standardized or empiric regimens which may include ineffective agents.[102,106] In cases where DST results for a child are unavailable, DST results for the presumed source case should be used to guide initial choice of regimen **(strong, moderate).**[23,102] For treatment of MDR-TB, a minimum of five drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs **(strong, moderate).**[23,102] Children with extensive or disseminated disease should be treated with at least five active drugs, because early aggressive treatment provides the best chance for cure.[82,83,102,107] When molecular or phenotypic DST demonstrates susceptibility (or is presumed based on the putative source case), a late-generation fluoroquinolone should be included in treatment regimens for MDR-TB **(strong, moderate).**[85,102] Recommendations on designing an individualized regimen for MDR-TB are provided in updated guidance.[102] Due to medication-related toxicity and modest efficacy, current guidance recommends avoiding injectable agents for routine MDR-TB care.[102] Injectable agents should be reserved for situations requiring injectables to assemble five effective drugs; amikacin or streptomycin should only be considered for inclusion in the regimen if there is documented susceptibility and an effective regimen cannot otherwise be constructed **(strong, moderate).**[102] Kanamycin and capreomycin should be avoided as these drugs have been associated with increased toxicity and adverse treatment outcomes **(strong, moderate).**[102] Bedaquiline, now increasingly a priority medication for treatment of MDR-TB in adults and children, has clinically significant drug–drug interactions with ART that should be considered when treating MDR-TB in the context of HIV. Co-treatment of TB with bedaquiline and HIV with EFV results in clinically significantly lower bedaquiline levels.[102,108] Co-treatment with lopinavir/ritonavir, specifically, and other boosted PIs, generally, can result in increased bedaquiline levels, although the clinical relevance is not clear.[109-111] Co-treatment of HIV with EFV or lopinavir/ritonavir and TB with delamanid does not result in clinically significant drug–drug-interactions.[112] All treatment for MDR-TB in children with HIV should be given daily with DOT **(strong, low).**[23,85,102]

### Extensively Drug-Resistant TB

In 2021, the definition of XDR-TB was updated.[27,28] WHO defines XDR-TB as caused by *M. tuberculosis* strains that fulfill the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (e.g., bedaquiline or linezolid); CDC has also updated the United States definition of XDR-TB. CDC defines XDR as TB caused by *M. tuberculosis* strains that are resistant to isoniazid, rifampin, a fluoroquinolone and a second-line injectable agent (e.g., amikacin, capreomycin, and kanamycin).[28] CDC also considers *M. tuberculosis* strains resistant to isoniazid, rifampin, a fluoroquinolone, bedaquiline, and linezolid to be XDR.[28] Children with suspected or confirmed XDR-TB should be managed in consultation with an expert.

XDR-TB is a form of MDR-TB for which the principles of management are similar, albeit with even greater challenges.[83,102]

## *Adjunctive Treatment*

Adjunctive treatment with corticosteroids is indicated for children with TBM **(strong, moderate),** as evidence suggests that it reduces mortality and long-term neurologic impairment in patients with TBM.[113,114] Adjunctive corticosteroids can also be considered for management of patients with severe IRIS, airway compression, pleural effusion, or pericarditis **(expert opinion).** Adjunctive corticosteroid use appears to reduce long-term constrictive complications in TB pericarditis[115] and is associated with more rapid symptom resolution in TB pleural effusion (relative indication).[116] Prednisone (1–2 mg/kg body weight/day) for 4 to 6 weeks is advisable, with tapered dosing during the final 2 weeks.

Treatment with isoniazid or cycloserine can result in neurologic adverse events, which are related to relative pyridoxine deficiency. Prophylaxis with pyridoxine has been recommended in at-risk patients for decades.[117] Recent evidence supports the idea that children with nutritional deficiencies and those with HIV are at particular risk of isoniazid-associated neuropathy.[118,119] Pyridoxine (1–2 mg/kg body weight/day, maximum 50 mg/day) is recommended for all children with HIV treated with isoniazid or cycloserine **(expert opinion).**

## *Monitoring of Adverse Events (Including IRIS)*

Regular monitoring of clinical and bacteriologic response to therapy is important. For children with pulmonary TB, chest radiographs should be obtained 2 months after the start of treatment to evaluate acute response to therapy **(expert opinion).**[23,45] Hilar adenopathy may persist or even worsen despite successful treatment, and normalization of the chest radiograph is not a criterion for shortening or discontinuing therapy.[23,45] The most important indicators of treatment response are bacteriologic conversion, symptom resolution, and weight gain. All children with culture-confirmed disease should be monitored regularly for bacteriologic response.[45]

Gastric upset can occur during the initial weeks of isoniazid treatment; however, this can usually be avoided when the medication is given with food. While the overall incidence of hepatoxicity is low, it is the most common serious adverse effect of isoniazid treatment. This toxicity includes subclinical hepatic enzyme elevation, which usually resolves spontaneously during continuation of treatment, and clinical hepatitis that usually resolves when the drug is discontinued. Drug-induced hepatic failure is rare, but the likelihood increases when isoniazid is continued despite hepatitis symptoms (jaundice or tender, enlarged liver). Hepatotoxicity is less frequent in children than in adults, but no age group is risk free.[78,89] Among children receiving isoniazid, 3% to 10% experienced transient asymptomatic serum transaminase elevations and <1% had clinical hepatitis; <1% of the cases required treatment discontinuation.[90,120] The rate of hepatotoxicity may be higher in children who take multiple hepatotoxic medications.[23]

Although the risk in children with HIV has not been quantified, excessive hepatotoxicity has not been documented. Routine monitoring of liver enzyme 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 (serum alanine aminotransferase at a minimum; aspartate aminotransferase and bilirubin also should be considered) should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (which is the same monitoring schedule as for ART initiated while a patient is receiving treatment for TB) **(expert opinion).**[23] Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, and more frequently if clinically indicated **(expert opinion).**[23] Patients and their families should be educated about the signs and symptoms of hepatotoxicity; for children who develop abnormal symptoms, treatment should be stopped immediately and an urgent evaluation for hepatotoxicity should be performed that includes measuring liver enzymes **(expert opinion).**[85] Mild elevations in serum transaminase concentration (i.e., less than 5 times the upper limit of normal [ULN]) do not require drug discontinuation in children who are asymptomatic and in whom other findings (including bilirubin) are normal **(expert opinion).**[45,85] If transaminase levels exceed five times the ULN or three times the ULN in the presence of any symptoms or signs indicative of hepatotoxicity (e.g., anorexia, jaundice, raised bilirubin), then hepatotoxic drugs should be discontinued immediately **(expert opinion).**[23] Discussion with an expert on further management using non-hepatotoxic drugs, and future careful re-challenge with first-line TB drugs should be considered.

Rifampin is also associated with hepatotoxicity. If transaminase levels exceed five times ULN or three times the ULN in the presence of any symptoms or signs indicative of hepatotoxicity (e.g., anorexia, jaundice, raised bilirubin), then all hepatotoxic drugs should be immediately discontinued **(expert opinion).** Discussion with an expert on further management using non-hepatotoxic drugs, and future careful re-challenge with first-line TB drugs should be considered. Rifampin causes color changes in body secretions including urine and saliva and may lead to discoloration of contact lenses. Ethambutol can cause optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, but it is rare at the recommended daily dose of 20 to 25 mg/kg body weight[23,45,85] and is usually reversible.[121,122] Because ethambutol should be given daily as part of a four-drug regimen for TB treatment, intermittent dosing (i.e., two or three times weekly) in children is not recommended **(expert opinion).** The maximum recommended dose of ethambutol given as daily dosing is 1.6 g/day **(expert opinion).** Use of ethambutol in very young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits.[23,45] Color vision screening should be performed prior to starting ethambutol for children who are old enough to cooperate with testing.

Other TB drugs have known side effects which should be monitored.[23,45,102] Hypothyroidism has been associated with ethionamide and 4 (para)-aminosalicylic acid. Major adverse effects of aminoglycoside drugs are ototoxicity[123] and nephrotoxicity. Ototoxicity can progress after termination of prolonged aminoglycoside use, and monitoring may be needed for 6 months after treatment completion. QT interval prolongation is an adverse effect of many new and newly repurposed medications used for MDR-TB treatment, including bedaquiline, delamanid, clofazimine, and the fluoroquinolones, especially moxifloxacin.[124] Although the risk of severe QT interval prolongation ($\geq$500 ms) appears to be low, regular electrocardiogram monitoring should be considered, especially when multiple QT-prolonging medications are combined in regimens. Linezolid is associated with frequent dose and duration dependent adverse effects that can be severe, including cytopenias (anemia, neutropenia, thrombocytopenia) and peripheral neuropathy; careful monitoring, especially for cytopenias in children, should be considered.

## *Immune Reconstitution Inflammatory Syndrome*

TB IRIS after initiation of ART was first reported in adults with HIV, and data on TB IRIS among children with HIV remains limited.[125-128] TB IRIS may present with new onset of systemic symptoms, especially high fever, expanding CNS lesions, and worsening adenopathy, pulmonary infiltrates, or pleural effusions.[90,129,130] IRIS should be suspected in children with advanced immunosuppression who develop new symptoms shortly after ART is initiated (within 3–6 months), despite evidence of good HIV control (increased weight and CD4 count, reduced viral load). TB IRIS represents a temporary exacerbation of symptoms and occurs in two clinical scenarios. In patients who have occult TB before ART initiation, TB may be unmasked by subsequent immune recovery.[131] This unmasking or incident TB IRIS usually occurs within 3 months of ART initiation, and the pathogen typically is detectable.[132] TB IRIS also can result in paradoxical clinical worsening of TB disease after ART initiation in patients with TB/HIV coinfection; treatment failure because of microbial resistance or poor adherence also must be excluded in these cases. In prospective observational studies, IRIS occurred in nearly 5% to 10% of children, usually within 4 weeks of ART initiation, resulting mostly from atypical mycobacteria, BCG (in young vaccinated infants) and TB (more prevalent in older children).[133,134] Mild-to-moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory agents, while short-term use of systemic corticosteroids can be considered in more severe cases **(expert opinion)**[125-128,135,136]; treatment for TB and ART should not be discontinued.

## *Managing Treatment Failure*

Most children with TB, including those with HIV, respond well to standard treatment. If clinical response is poor, then adherence to therapy, drug absorption, and the possibility of drug resistance should be carefully considered. Mycobacterial culture, DST, and assessment of serum concentrations of TB drugs should be done whenever possible. Drug resistance should be suspected in any child whose smear or culture fails to convert from positive to negative after 2 months of DOT, and alternative diagnoses or dual pathology should also be considered.

## *Preventing Recurrence*

TB recurrence can represent relapse or re-infection disease. The relapse rate is low in children with drug-susceptible TB who receive DOT and ART. Recurrence within 6 to 12 months of treatment completion should be regarded as relapse and managed the same as treatment failure **(expert opinion).** Recurrence more than 6 to 12 months after treatment completion might be due to re-infection with *M. tuberculosis*, especially after a new exposure to a person with TB disease or a visit to a TB-endemic setting. Re-infection should be managed the same as the first episode of TB disease. Regular TB exposure screening should continue after completion of treatment, and preventive therapy should be considered whenever repeat exposure occurs.

## *International Guidelines*

These guidelines were developed for the United States. Guidelines for resource-limited countries may be different and are available from WHO.[26]

## *Additional Resources*

- CDC Division of TB Elimination
  https://www.cdc.gov/tb
  800-CDC-INFO (800-232-4636)
  TTY: 888-232-6348
  24 Hours/Every Day
  cdcinfo@cdc.gov

- TB Centers of Excellence for Training, Education, and Medical Consultation
  https://www.cdc.gov/tb/education/tb_coe/default.htm
- Drug-Resistant Tuberculosis: A Survival Guide for Clinicians
  https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- WHO Ending TB in Children and Adolescents
  https://www.who.int/activities/ending-tb-in-children-and-adolescents
- International Union Against TB and Lung Disease Child & Adolescent TB website
  https://theunion.org/our-work/tuberculosis/child-adolescent-tuberculosis

## PICO Questions

### *Detection of Latent TB Infection*

**I. Among children <15 years old with HIV, do interferon-gamma release assays (IGRA) compared to tuberculin skin test (TST) reliably identify latent tuberculosis infection (LTBI)?**

IGRAs and TSTs can be used to diagnose LTBI in children 5 years or older **(strong, moderate).**[23] Although CDC guidelines currently recommend TSTs for diagnosing of LTBI in children 2 to 5 years old, some experts and the AAP Red Book recommend using IGRAs to diagnose LTBI in children ≥2 years old.[23,50] When applicable, IGRAs are preferable for diagnosing LTBI in Bacille Calmette-Guerin (BCG)–vaccinated people and those who are unlikely to return for interpretation of TST results **(strong, moderate).**[50] However, younger age (<5 years), HIV itself, and lower CD4 cell counts have been associated with indeterminate IGRA results (and false negative TST results). CDC guidelines and the AAP Red Book recommend TSTs for diagnosing LTBI in children <2 years old **(expert opinion).**[23,50]

Diagnostic methods for LTBI include the TST administered by the Mantoux method using 5 tuberculin units of an FDA-approved purified protein derivative, or an FDA-approved IGRA (QuantiFERON-TB Gold, QuantiFERON-Plus, and T-SPOT.*TB*). Evidence suggests that TST and IGRAs have comparable sensitivity in immune-competent adults.[50]

**II. Among children <15 years old with HIV, does a negative TST or IGRA reliably exclude TB infection or disease?**

Neither TST nor IGRA results can definitively exclude LTBI or TB disease **(strong, moderate).**

A negative result by either TST or IGRA does not exclude *M. tuberculosis* infection or TB disease, especially in the context of HIV infection.[23,53] AAP reports that 10% to 40% of children with TB disease who are immunocompetent do not react to a TST; TST reactivity has been shown to be even lower among those with HIV, particularly in the context of low CD4 counts and severe malnutrition.[48] IGRAs and TSTs have similar sensitivities; however, because IGRAs can distinguish between BCG and *M. tuberculosis*, they have higher specificity in many clinical settings.[23] Clinicians should screen for possible exposure to TB disease through a detailed history and for signs of TB disease through a physical exam. Documentation of exposure to an infectious source of TB disease should prompt further diagnostic investigation and, regardless of TST or IGRA result, may prompt a decision to treat for TB infection or TB disease.

## *Treatment*

### Treatment for Latent TB Infection

**III. Among children <15 years old with HIV, does LTBI treatment result in fewer cases of TB disease, compared to no treatment?**

LTBI treatment is highly effective for preventing TB disease. Therefore, after 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).**[23,46]

Young children and children with HIV who acquire TB have a high rate of progression to active disease. Studies have demonstrated that treatment of TB infection with isoniazid greatly diminishes the likelihood of progression to TB disease[66,70,71,136]; on a population level, screening for and treatment of LTBI should result in fewer TB cases over time.[66] Although isoniazid has been shown to prevent TB disease among those with known TB exposure or TB infection, evidence does not support its use for primary prevention in infants with low risk of TB exposure, such as in low incidence settings like the United States. One randomized controlled trial evaluated the use of isoniazid for **primary** prevention of TB infection and disease in infants with and without HIV who had no known TB exposure and showed no difference in TB incidence, infection, or death.[26]

**IV. 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?**

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 regimen for treatment of LTBI can be used in adults and children ≥2 years old with HIV who are receiving ART regimens with acceptable drug–drug interactions with rifapentine **(strong, moderate).**

A 12-dose combination regimen of once-weekly isoniazid and rifapentine appears to be as safe and effective as other regimens in preventing TB disease, and the completion rate is greater than for regimens of longer duration.[46,71,73,75] There are no commercially available dispersible formulations of rifapentine and dosing has not yet been determined for children <2 years old. The experience in children with HIV is limited and drug interactions between weekly rifapentine and many antiretroviral drugs, including integrase strand transfer inhibitors (INSTIs), have not yet been determined in children. For children ≥2 years old, when drug–drug interactions allow, the 12-dose combination regimen of once-weekly isoniazid and rifapentine is the preferred regimen. Daily isoniazid for 6 to 9 months can be used when drug interactions preclude the use of the preferred rifamycin-based preventive treatment regimens.

**V. 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?**

Some studies have demonstrated successful prevention of presumed drug-resistant TB through treatment of LTBI with regimens informed by the drug-susceptibility 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 ART might be necessary **(expert opinion).** After exposure to TB caused by organisms with other drug resistance patterns (e.g., MDR), expert consultation should be obtained to determine optimal LTBI treatment regimens. DST results for the TB index patient are important considerations in the management of children exposed to drug-resistant TB **(expert opinion).**[137]

The optimal prophylaxis regimen for children with HIV and exposure to or TB infection from a person with MDR-TB or XDR-TB has not been defined.[23,66,137] Treatment for that child's infection should be tailored in consultation with an expert. A guiding principle is to use therapy to which the source case demonstrated susceptibility, at a dose that is safe and effective in the child. There is evidence that rifampin is safe and effective at preventing TB disease in adults and children, and this would be the preferred agent if the source case was known to be resistant to isoniazid but susceptible to rifampin.[23,66,81,82,138,139] Rifampin, however, has drug–drug interactions with several antiretroviral drugs used to treat HIV infection, and dose adjustment may be needed.

## Treatment of TB Disease

### 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).**

In adults with HIV who are not on ART at the time of TB diagnosis, early initiation of ART reduces mortality, especially among those with CD4 counts below 50 cell/mm$^3$, but increases risk of IRIS.[92,94] Data for children, although limited, support early ART initiation, especially in those with severe immune suppression,[66,93] and WHO recommends that all children with HIV and TB disease who are not already receiving ART should begin ART within 8 weeks of starting TB treatment.[94,140] The recommended timing of ART initiation with TB involving the CNS remains more uncertain because of the potentially devastating effects of CNS IRIS.[96,97]

### 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).**

To effectively treat TB disease and diminish the risk of acquired drug resistance, it is important that patients adhere to proven treatment regimens, which generally require at least 6 months of treatment with multiple drugs. Sustained adherence is difficult for anyone, and this may be particularly true for young children. Some recent analyses have demonstrated that self-administered therapy compares favorably with DOT, but these studies did not include many children or adolescents, who represent a markedly different patient cohort for this intervention. The most relevant study for the United States was conducted in 1998 and showed that DOT was clearly associated with better treatment completion.[83] For this reason, DOT by a trained health care worker is recommended to maximize adherence.[23]

**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).**[23,45]

WHO recommends a standard treatment regimen for drug-susceptible TB disease in children with HIV, consisting of four-drug therapy for a 2-month intensive phase followed by a 4-month continuation phase of isoniazid and rifampin **(expert opinion).**[23,45,85] This guidance is supported by AAP. Alternative regimens have not been as well studied although some experts would consider a three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase followed by a continuation phase using isoniazid and rifampin for 4 months to be appropriate for children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB **(expert opinion).**[23,85]

**IX. Among children <15 years old with HIV who are taking isoniazid or cycloserine, should adjunctive pyridoxine versus no adjunctive pyridoxine supplementation be recommended routinely to improve clinical outcomes?**

Pyridoxine supplementation (1–2 mg/kg body weight/day, max 50 mg/day) is recommended for all children with HIV who are taking isoniazid or cycloserine **(expert opinion).**[23]

Treatment with isoniazid or cycloserine can result in relative pyridoxine deficiency and neurologic adverse events. For decades, prophylaxis with pyridoxine has been recommended for patients at risk of isoniazid neuropathy. Recent evidence supports the idea that children with nutritional deficiencies and those with HIV are at particular risk.[117,118] Consequently, adjunctive treatment with pyridoxine is recommended in these groups to reduce the likelihood of neurologic adverse events.[23]

**X. Among children <15 years old with HIV in whom TB disease is diagnosed, what evidence-based ART regimens result in better treatment outcomes?**

Among children weighing >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 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 (LPV/r)-based ART, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (RTV) **(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. Simultaneous treatment of TB disease and HIV infection is difficult, because of known drug interactions in the recommended regimens. Rifampin increases elimination of INSTIs through UDP-glucuronosyltransferase upregulation and therefore dose adjustments of both raltegravir and dolutegravir are needed during TB/HIV co-treatment.[141] Rifampin potently induces the CYP3A enzyme system, which increases metabolism of protease inhibitors and nevirapine; co-administration of rifampin requires dose adjustment of these antiretroviral drugs as well. Interactions between rifampin and efavirenz are less significant, allowing achievable serum levels of EFV without dose adjustment.[98]

DTG is one of the preferred first-line ART options for children with HIV ≥4 weeks or ≥3 kg, given its superior efficacy compared to PI- or non-nucleoside-based ART in adults.[142,143] Preliminary results from the ODYSSEY trial in children aged 6 to 18 years receiving TB treatment with rifampin demonstrated that twice-daily DTG dosing was safe and achieved adequate dolutegravir pharmacokinetic targets.[80] Therefore, in children >20 kg, DTG-based ART is the preferred regimen in the context of TB/HIV co-treatment, with 50 mg DTG given twice daily throughout TB treatment. While the FDA has approved twice-daily DTG during TB treatment for children as young as 4 weeks old and ≥3 kg, additional evidence on safety and PK parameters in children <20 kg is needed to inform formal U.S. Department of Health and Human Services recommendations.[99] There are insufficient pharmacokinetic data for the use of bictegravir during TB treatment for children with HIV.

For children <20 kg who are receiving a RAL-based regimen, RAL dosing should be increased to 12 mg/kg twice daily for the duration of TB treatment. Safety and adequate PK targets in children receiving RAL 12 mg/kg twice-daily dosing with concurrent rifampin administration have been demonstrated among children as young as 4 weeks of age.[81,100] For children <20 kg receiving a LPV/r-based regimen, the dose of RTV should be increased to achieve a 1:1 ratio between LPV and RTV. Non-inferiority of super-boosted LPV/r PK targets during rifampin treatment was demonstrated in a clinical trial of South African children between 3 to 15 kg receiving rifampin for TB treatment.[101]

Efavirenz maintains serum levels better than nevirapine when co-administered with anti-TB therapy; as such, regimens that contain efavirenz are preferred compared to nevirapine-based regimens in the setting of TB/HIV.[144,145]

There have been no head-to-head comparisons of ART on treatment outcomes during TB/HIV co-treatment. A high proportion of young children (11 of 12) achieved virologic success (>1 log decrease or viral load <400 copies/mL) in a trial of super-boosted LPV/r during TB co-treatment, but few children (2 of 12) achieved a more stringent definition of viral suppression (<50 copies/mL).[80] Lower rates of virologic suppression during the TB/HIV co-treatment period were observed in a trial of children on EFV-based therapy.[146] For this reason, in the United States, therapeutic drug monitoring should be used to guide dose adjustments to antiretroviral treatment and close virologic monitoring during TB/HIV co-treatment is recommended; consultation with an expert experienced in treatment of TB and HIV in children is also recommended.[23,147]

### 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).**[23]

Extrapulmonary TB disease, especially involving the CNS or bones and joints, can be associated with higher morbidity or mortality. Additionally, extrapulmonary TB of the CNS or bones and joints can be more difficult to treat because drug penetration into infected tissues or spaces is often reduced. As a consequence, the treatment should be extended to 12 months (a 2-month intensive phase, followed by a 10-month continuation phase) **(expert opinion).**[23,85] A recent prospective cohort demonstrated good results treating meningeal TB with conventional regimens (substituting ethionamide for ethambutol)[90]; but this study did not have a comparison to longer treatment, and the results have not been validated with repeat investigation. Given the potentially dire consequences of insufficiently treated disease, the recommendation for 12 months of treatment remains unchanged.

### 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).**[23]

For TBM, some experts recommend adding a fluoroquinolone to the treatment regimen pending the results of DST **(expert opinion).**

TBM is a potentially devastating disease, associated with high morbidity and mortality. It is critical that the most effective agents are used during treatment. This requires drugs that are both effective against the organism and able to penetrate the blood–brain barrier. Ethionamide has been shown to cross the blood–brain barrier in higher concentrations than ethambutol and is recommended for the treatment of TBM in adults and children.[23,88]

### XIII. Among children <15 years old with HIV who are diagnosed with TBM, pericardial or pleural effusion, airway compression, or severe IRIS, 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 IRIS, airway compression, pleural effusion, or pericarditis **(expert opinion).**

In children with certain forms of extrapulmonary TB disease, particularly TBM and TB-related pleural or pericardial effusions, the inflammatory response to disease can cause severe deleterious clinical consequences. Corticosteroids reduce the exuberance of the inflammatory response but may also diminish the immune response to disease. Evidence strongly suggests that adjunctive treatment with corticosteroids reduces mortality and disabling neurologic deficits in patients with TBM[112,113]; one systematic review has suggested that corticosteroids may reduce mortality in any form of TB,[148] but additional evidence is needed. While a mortality benefit has not been clearly demonstrated for other forms of TB disease, adjunctive corticosteroids have been shown to reduce constrictive pericarditis in patients with TB pericarditis and are associated with more rapid symptom resolution in TB pleural effusion.[114,115,127,149] There are limited data on the use of corticosteroids in children, and these recommendations are largely based on studies involving adults.

### 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?

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).** 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 are not available for the child) **(strong, moderate).**

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).**[137]

Treatment of drug-resistant TB disease can be complex, and consultation with an expert in drug-resistant TB is important. When the disease-causing organism is resistant to both isoniazid and rifampin, the two most active agents against *M. tuberculosis*, treatment requires multiple alternative agents, which often have compounding toxicities and are less effective, requiring prolonged therapy for up to 24 months. Using agents that have been shown by DST to have efficacy is clinically meaningful and associated with better treatment success allowing clinicians to tailor regimens appropriately.[102,104,105,137] For these reasons, clinicians are advised to treat drug-resistant TB based on DST results for the infecting organism or the DST results from the organism of the presumed source case.[23,137] In all cases of MDR-TB in children with HIV, at least five drugs to which the infecting organism is known or presumed to be susceptible should be used, including two or more bactericidal drugs.[23,137] For children with a TB strain resistant to only isoniazid, isoniazid should be discontinued, and experts recommend the use of rifampin, pyrazinamide, and ethambutol for six months or up to nine months; a late-generation fluoroquinolone should also be added to the treatment regimen.[137] Late-generation fluoroquinolones are key components of current MDR-TB treatment approaches, and in almost all cases should be included as part of a treatment regimen for MDR-TB, in consultation with a clinical expert.[85]

**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 enzyme 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 5 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).**

While the overall incidence of hepatotoxicity is low, it is the most common serious adverse effect during treatment of TB disease. This toxicity includes subclinical hepatic enzyme elevation, which usually resolves spontaneously during continuation of treatment, and clinical hepatitis that usually resolves when the drug is discontinued. Hepatotoxicity rarely progresses to hepatic failure, but the likelihood increases when isoniazid is continued despite hepatitis symptoms (jaundice; tender, enlarged liver). Hepatotoxicity is even less frequent in children than in adults,[77,150] but no age group is risk free. The rate of hepatotoxicity may be higher in children who take multiple hepatotoxic medications. There is a lack of data comparing the clinical consequences of routine versus clinically directed measurement of liver enzymes, and no studies which conclusively demonstrate that routine measurements reduce the incidence of liver disease in children on antituberculosis therapy. AAP recommends routine liver transaminase monitoring for children receiving ART.[23,85] Mild elevations in serum transaminases do not require drug discontinuation.[85]

**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 children in whom TB is diagnosed should be tested for HIV infection **(expert opinion).**

WHO and CDC both recommend routine HIV testing for all people in whom TB disease is diagnosed given the increased risk of disease among those who are immunocompromised.[45,85] WHO explicitly recommends HIV testing for children as the diagnosis of HIV has important implications for the management of both TB and HIV. Excluding HIV infection also has implications for confirming the clinical diagnosis of TB.[85]

## Dosing Recommendations for Preventing and Treating TB in Children with HIV

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment of LTBI<br><br>*Also Known as TB Preventive Therapy* | Source Case Drug Susceptible<br><br>*Age 2 to <12 years*<br><br>• 12 weekly doses of isoniazid (25 mg/kg for children aged 2–12 years) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum)<br><br>*Age ≥12 years*<br><br>• 12 doses of weekly isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum)<br><br>Source Case Drug Resistant<br><br>• For isoniazid-resistant source cases, daily rifampin 15–20 mg/kg (maximum 600 mg/day) for 4 months is recommended.<br><br>• For isoniazid- and rifampin-resistant (i.e., MDR-TB) source cases, consult a TB expert and local public health authorities. | Rifampin 15–20 mg/kg (max 600 mg) daily for 4 months duration<br><br>*or*<br><br>Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 15–20 mg/kg (maximum 600 mg/day) for 3 months duration<br><br>*or*<br><br>Isoniazid 10–15 mg/kg (max 300 mg) daily for 6–9 months | Indications<br><br>• Positive TST (TST ≥5 mm in children with HIV) or IGRA without previous TB treatment<br><br>• Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis)<br><br>Considerations<br><br>• TB disease must be excluded before starting treatment for latent TB infection.<br><br>• Drug-drug interactions with ART should be considered for all rifamycin-containing alternatives.<br><br>Criteria for Discontinuing Prophylaxis<br><br>• Only with documented severe adverse event, such as hepatotoxicity, hypersensitivity, or other adverse drug reactions, which are rare in children and adolescents.<br><br>Adjunctive Treatment<br><br>• Pyridoxine 1–2 mg/kg body weight once daily (maximum 25–50 mg/day) with isoniazid; pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all children with HIV; and pregnant adolescents and adults. |

## Dosing Recommendations for Preventing and Treating TB in Children with HIV

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment of TB Disease | Intrathoracic Disease<br>*Drug-Susceptible TB*<br>• Intensive Phase (2 Months)<br>o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus**<br>o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily, **plus**<br>o Pyrazinamide 30–40 mg/kg body weight (maximum 2 g/day) by mouth once daily, **plus**<br>o Ethambutol 15–25 mg/kg body weight (maximum 1 g/day) by mouth once daily<br>o In children with minimal disease with fully drug-susceptible TB, some experts recommend a three-drug intensive phase regimen excluding ethambutol.<br>• Continuation Phase (4 Months)<br>o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus**<br>o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily<br>Extrathoracic Disease<br>Note: Depends on disease entity<br>• Lymph node TB—treat as minimal intrathoracic disease<br>• Bone or joint disease—consider extending the continuation phase to 10 months (for total duration of therapy of 12 months). | Alternative for Rifampin<br>• Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if three times a week)<br>• Discuss with an expert.<br>Alternative Continuation Phase with Three Times Weekly Dosing<br>*If Good Adherence and Treatment Response (4 months)*<br>• Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth three times per week, **plus**<br>• Rifampin 15–20 mg/kg body weight (maximum 600 mg/day) three times per week<br>• In children with minimal disease with fully drug-susceptible TB, some experts recommend a continuation phase of 4 months (total duration of therapy of 6 months). | Treatment for TB disease should always be provided by DOT.<br>If ART-naive, start TB therapy immediately and initiate ART within 2 to 8 weeks.<br>If already on ART, review regimen to minimize potential toxicities and drug interactions; start TB treatment immediately.<br>Potential drug toxicity and interactions should be reviewed at every visit. Drug interactions with ART should be considered for all rifamycin-containing alternatives.<br>Adjunctive Treatment<br>• Co-trimoxazole prophylaxis<br>• Pyridoxine 1–2 mg/kg body weight/day (maximum 25–50 mg/day) with isoniazid or cycloserine/terizidone, if malnourished. Pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all children with HIV; and pregnant adolescents and people.<br>• Corticosteroids (2 mg/kg body weight per day of prednisone [maximum 60 mg/day] or its equivalent for 4–6 weeks followed by tapering) with TB meningitis; may be considered with pleural effusions, pericarditis, severe airway compression, or severe IRIS. |

## Dosing Recommendations for Preventing and Treating TB in Children with HIV

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| | TB Meningitis<br>• As an alternative to ethambutol, streptomycin 20–40 mg/kg body weight (maximum 1 g/day) IM once daily. During intensive phase, consider ethionamide 15–20 mg/kg body weight by mouth (maximum 1 g/day), initially divided into two doses until well tolerated.<br>• Many experts recommend rifampin doses of 20–30 mg/kg daily for treatment of TB meningitis. See the AAP Red Book and WHO Operational Handbook on Tuberculosis for more information.<br>• Consider extending the continuation phase to 10 months (for a total duration of therapy of 12 months).<br>• Discuss with an expert.<br>Drug-Resistant TB<br>• Therapy should be based on the resistance pattern of the child (or of the source case where the child's isolate is not available); consult an expert. | | Second-Line Drug Doses<br>• Consult with an expert as dosing guidelines continue to evolve with emerging data. |

[a] Some experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers.

Key: AAP = American Academy of Pediatrics; ART = antiretroviral therapy; ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy; ERS = European Respiratory Society; IDSA = Infectious Diseases Society of America; IGRA = interferon-gamma release assay; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent TB infection; MDR-TB = multidrug-resistant TB; TB = tuberculosis; TST = tuberculin skin test; WHO = World Health Organization

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

## Panel's Recommendations

Prevention of Primary Exposure

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

Chemoprophylaxis

- Chemoprophylaxis is highly effective in preventing PCP. Prophylaxis is recommended for all HIV-infected children aged ≥6 years who have CD4 T lymphocyte (CD4) cell counts <200 cells/mm$^3$ or CD4 percentage <15%, for children aged 1 to <6 years with CD4 counts <500 cells/mm$^3$ or CD4 percentage <15%, and for all HIV-infected infants aged <12 months regardless of CD4 count or percentage **(AII)**.
- Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be HIV-uninfected or presumptively HIV-uninfected **(AIII)**. HIV-infected infants should be administered prophylaxis until age 1 year, at which time they should be reassessed on the basis of the age-specific CD4 count or percentage thresholds mentioned above **(AII)**.
- Trimethoprim–sulfamethoxazole (TMP–SMX; cotrimoxazole), administered either on 3 consecutive days/week or daily, is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(AI)**.
- Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone **(AI)** or dapsone **(BI*)**.
- Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and who are old enough to use nebulization with a 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 ≥15% or CD4 count is ≥200 cells/mm$^3$ for patients aged ≥ 6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm$^3$ for patients aged 1 to <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 **(AI)**. As the acute pneumonitis subsides, children with mild-to-moderate disease who do not have malabsorption or diarrhea can be transitioned to oral treatment with the same total daily dose of TMP-SMX administered in 3 or 4 divided doses to complete a 21-day course **(AII)**.
- IV pentamidine isethionate once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy **(AI*)**.
- Atovaquone is an alternative for treatment of mild-to-moderately severe PCP **(BI*)**.
- Dapsone/TMP is effective in treating mild-to-moderate PCP **(BI*)**.
- Clindamycin/primaquine has been used to treat mild-to-moderate PCP; data in children are unavailable **(BIII)**.
- A short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis **(AI*)**.
- Patients who have experienced an episode of PCP should continue on PCP prophylaxis after completion of treatment until CD4 counts exceed the threshold for initiating prophylaxis **(AI)**.
- Children who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite normal or high CD4 counts or percentages **(BI*)**.

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

***Rating of Evidence:*** *I = One or more randomized trials in children† 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*

## Epidemiology

*Pneumocystis* spp. are found worldwide in the lungs of humans and lower animals. The organisms are host specific, and cross-infection between humans and other species does not occur. *Pneumocystis* spp. from all sources are morphologically, tinctorially, and biologically similar, but surface antigens and gene sequencing have demonstrated host-specific differences. Since the original designation of *Pneumocystis carinii* a century ago, several changes in terminology have been suggested. The most recent proposal was to change *P. carinii* to *Pneumocystis jirovecii* for isolates from human lungs. *Pneumocystis* has been designated a fungus on the basis of DNA analysis, but it has several biologic features of protozoa. Most humans are infected with *Pneumocystis* early in life. By ages 2 to 4 years, more than 80% of children in most countries have acquired antibodies to *Pneumocystis*.[1-3] Immunocompetent infants with the infection are either asymptomatic or have mild respiratory symptoms. *Pneumocystis jirovecii* pneumonia (PCP) occurs almost exclusively in the immunocompromised host.

PCP remains an important AIDS-indicator disease among HIV-infected children. The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at ages 3 to 6 months.[4-6] Data from the Centers for Disease Control and Prevention Pediatric Spectrum of Disease Project (1994–2001) indicate a decline in PCP infection rates (cases per 1000 HIV-infected children) from 25 in 1994 to 18 in 1996 to 6 in 2001.[7] Similarly, analyses of data from the Perinatal AIDS Collaborative Transmission Study revealed a 95% decline in PCP (cases per 100 child-years) from 5.8 (pre-combination antiretroviral therapy [cART] era) to 0.3 (cART era).[8] Finally, the incidence rate for PCP (cases per 100 child-years) was 1.3 during the pre-cART era (1981–1988) and <0.5 during the cART era (2001–2004).[9] This decline probably resulted from implementation of interventions to prevent mother-to-child transmission of HIV, introduction of cART in HIV-infected children in 1995, and chemoprophylaxis for PCP.

PCP continues to be a major cause of death among HIV-infected infants and children in the developing world. Autopsies done in Africa revealed PCP in 16% of children who died with HIV/AIDS during 1992 and 1993,[10] in 29% of those who died during 1997 and 2000,[11] and in 44% of those who died during 2000 and 2001.[12]

The mode of transmission of *Pneumocystis* among HIV-infected infants, children, and adults is not firmly established, but airborne human-to-human transmission is likely. Animal studies show *Pneumocystis* is transmitted by air from infected to susceptible rats.[13,14] Furthermore, *Pneumocystis* can infect normal mice, produce subclinical disease and be transmitted to normal or immunocompromised mice.[15] Human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases in recent studies.[16-18] Intrauterine transmission is considered rare. However, in one report, 1 of 8 infants born to women who had AIDS and PCP during pregnancy had evidence of *Pneumocystis* infection.[19]

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

## Clinical Manifestations

Prominent clinical features of PCP among HIV-infected children are fever, tachypnea, dyspnea, and cough. The severity of these signs and symptoms varies from child to child. Onset can be abrupt or insidious with nonspecific symptoms such as mild cough, dyspnea, poor feeding, diarrhea, and weight loss. Some patients may not be febrile, but almost all will have tachypnea by the time pneumonitis is evident on chest radiograph. Physical examination sometimes shows bilateral basilar rales with evidence of respiratory distress and hypoxia.

In HIV-infected children with pneumonia, four clinical variables are independently associated with PCP: aged <6 months, respiratory rate >59 breaths per minute, arterial percentage hemoglobin saturation ≤92%, and absence of vomiting.[20] A high plasma HIV RNA concentration strongly predicts PCP and other opportunistic infections (OIs).[21]

Extrapulmonary *Pneumocystis* organisms, often associated with a localized inflammatory reaction, are found in <2.5% of HIV-infected adults and children.[22,23] This can occur without concurrent PCP and can be located at multiple noncontiguous sites. Involved sites have included ear, eye, thyroid, spleen, gastrointestinal (GI) tract, peritoneum, stomach, duodenum, small intestine, transverse colon, liver, and pancreas. Less frequently involved sites include adrenal glands, muscle, bone marrow, heart, kidney, ureter, lymph nodes, meninges, and cerebral cortex.

## Diagnosis

Most children with PCP have substantial hypoxia with low arterial oxygen pressure ($PaO_2$ typically <70 mm Hg) and an A-a gradient >30 mmHg. CD4 percentage is often <15% and CD4 counts are usually <200 cells/mm$^3$ in children aged 6 years and older. Lactic dehydrogenase is often increased, but this is not specific for PCP. Serum albumin may be depressed. Chest radiographs most commonly reveal bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance, but they also can be normal or have only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally before reaching the apical portions of the lung. Rarely, lobar, cavitary, nodular, or miliary lesions; pneumothorax; or pneumomediastinum are observed.

A definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids in the presence of pneumonitis. Diagnostic procedures are the same as for adults suspected of having PCP (see *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults*),[24] but some procedures may be more difficult to perform in children.

Induced sputum analysis, during which the patient produces sputum after inhalation of nebulized 3% hypertonic saline, may be difficult in children aged <2 years because of small airways and poor ability to produce sputum. Complications from the procedure include nausea, vomiting, and bronchospasm. Sensitivity of sputum analysis in adults ranges from 25% to 90%. After a negative induced sputum sample, a bronchoalveolar lavage may be necessary for definitive diagnosis.

Nasogastric aspirates, if positive, are of diagnostic value. *Pneumocystis* organisms were found in 48.6% of HIV-infected children with respiratory illnesses in whom gastric aspirates were obtained on three consecutive mornings.[25] Other studies have shown the organism only found in gastric contents of patients with PCP.[26]

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

Fiberoptic bronchoscopy with trans-bronchial biopsy is recommended only when bronchoalveolar lavage is negative or non-diagnostic despite a clinical picture consistent with PCP. Sensitivity is 87% to 95%, and cysts can typically be identified up to 10 days after initiation of treatment. Complications include pneumothorax and hemorrhage; this procedure is contraindicated in children with thrombocytopenia.

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

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

Polymerase chain reaction assays to amplify the human *Pneumocystis* MSG/gpA gene, mitochondrial large subunit (mtLSU) RNA, the dihydropteroate synthase gene, and the internal transcribed spacer region genes have been developed for diagnostic evaluation. These tests are usually more sensitive but less specific than microscopic methods and are not standardized or available in most centers.[27,28] *Pneumocystis*-specific DNA is found in 18% of bronchoalveolar lavage samples from patients without clinical PCP, HIV, or other infections.[29]

Coinfection with other organisms such as cytomegalovirus (CMV) or pneumococcus has been reported in HIV-infected children.[6,30,31] Children with dual infections may have more severe disease. Although CMV in lung secretions of children with PCP indicates colonization, it usually does not require therapy in the absence of histopathologic evidence of invasive CMV disease.

## Prevention Recommendations

### *Preventing Exposure*

Clinical data are unavailable upon which to make a decision regarding isolation of patients with PCP. However, animal model experiments, which generally provide an accurate demonstration of the pathophysiology seen in humans, suggest that transmission occurs easily; therefore, isolation should be strongly considered **(AIII)**.[32] Immunocompromised patients who are compliant with PCP prophylaxis, especially with trimethoprim-sulfamethoxazole (TMP-SMX), are unlikely to acquire PCP. However, some experts still suggest that such at-risk patients not be placed in a room with another patient with PCP. Caution is also advised in having an at-risk patient share a room with another patient with an undiagnosed respiratory illness that could be PCP **(AIII)**. This is especially true of respiratory illnesses occurring during the first 2 years of life when 85% of children undergo a primary infection with *Pneumocystis*.[1]

### *Preventing First Episode of Disease*

Chemoprophylaxis is highly effective in preventing PCP. Criteria for its use are based on a patient's age and CD4 count or percentage.[33] Prophylaxis is recommended for all HIV-infected children aged ≥6 years who have CD4 counts <200 cells/mm$^3$ or CD4 percentage <15%, for children aged 1 to <6 years with CD4 counts <500 cells/mm$^3$ or CD4 percentage <15%, and for all HIV-infected infants aged <12 months regardless of CD4 count or percentage **(AII)**.[33]

Infants born to HIV-infected mothers should be considered for prophylaxis beginning at 4 to 6 weeks of age. 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 previously **(AII)**.[34] Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be definitively HIV-uninfected[34] or presumptively HIV-uninfected **(AIII)**.[35-37] Prophylaxis is not recommended for infants who meet criteria for being definitively or presumptively HIV-uninfected. In non-breastfeeding infants with no positive HIV virologic test results, presumptive exclusion of HIV infection can be based on two negative virologic test results, one obtained at ≥2 weeks and one obtained at ≥4 weeks of age; one negative virologic test result obtained at ≥8 weeks of age; or one negative HIV-antibody test result obtained at ≥6 months of age. Definitive exclusion of HIV infection is based on two negative virologic test results: 1 obtained at ≥1 month of age and one obtained at ≥4 months of age, or on 2 negative HIV-antibody test results from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, a child should have no other laboratory (e.g., no positive virologic test results) or clinical conditions (e.g., no AIDS-defining conditions that cannot be explained on the basis of other causes of immunosuppression) or evidence of HIV infection.[35-37]

Four drug regimens have been found effective and relatively safe for preventing PCP in high-risk HIV-infected children and adults.

TMP–SMX (cotrimoxazole) is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(AI)**.[38-40] TMP alone has little, if any, anti-*Pneumocystis* activity, but it enhances the activity of the sulfonamide. The prophylactic dosage is 150 mg/$m^2$ body surface area per day TMP and 750 mg/$m^2$ body surface area per day SMX (approximately 5.0–10 mg/kg body weight per day TMP and 25–50 mg/kg body weight per day SMX; dosing based on TMP component) administered orally either every day **(AI)**[41] (5.0–10 mg/kg body weight/dose once daily TMP and 25–50 mg/kg body weight/dose once daily SMX) or on 3 consecutive days per week (2.5–5.0 mg/kg body weight/dose TMP and 12.5–25 mg/kg body weight/dose SMX twice per day)[42] or every other day (e.g., Monday, Wednesday, Friday). The total daily dose should not exceed 320 mg TMP and 1600 mg SMX. In patients with impaired renal function, a reduced dose may be necessary.

TMP-SMX, preferably given daily, also is effective in preventing toxoplasmosis[43] and some bacterial infections (e.g., *Salmonella*, *Haemophilus*, *Staphylococcus*).[41,44-46]

Dihydropteroate synthase gene mutations in *Pneumocystis* from humans have been observed with TMP-SMX and dapsone prophylaxis, suggestive of possible drug resistance, but studies for clinical correlates have not provided conclusive results.[27] More apparent is the association of prolonged TMP-SMX prophylaxis for PCP with the emergence of TMP-SMX resistant bacterial species due to selective pressure, a point to be considered in managing bacterial infections in patients receiving prophylaxis.[47,48]

Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone **(AI)**[49] or dapsone **(BI*)**.[39] Atovaquone is effective and safe but expensive. Dapsone is effective and inexpensive but associated with more serious adverse effects than atovaquone.

Atovaquone is administered with a meal as an oral yellow suspension as a single daily dose of 30 mg/kg body weight/day for patients aged 1 to 3 months and >24 months to 12 years, as 45 mg/kg body weight/day for infants aged >3 months to 24 months,[50] and as 1500 mg (10 cc) for adolescents and adults aged ≥13 years **(BI*)**.[39,40] Outcomes with atovaquone equaled those of dapsone for the prevention of PCP in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both.[39] Unlike TMP-SMX, atovaquone has no antibacterial activity but is effective against *Toxoplasma gondii*. Azithromycin, in a single dosage of 5.0 mg/kg body weight/day, has been used to supplement atovaquone for greater broad-spectrum prophylaxis. The randomized, double-blind, placebo-controlled study the Pediatric AIDS Clinical Trial Group (PACTG) 254 compared TMP-SMX and atovaquone plus azithromycin for 3 years (median) in 366 HIV-infected children qualifying for PCP prophylaxis.[49] Results showed atovaquone-azithromycin to be as effective as TMP-SMX for preventing serious bacterial infections, as well as PCP.

Dapsone can be administered on a daily or weekly schedule as 2.0 mg/kg body weight/day (maximum total dosage 100 mg/day) or 4.0 mg/kg body weight/week (maximum total dosage 200 mg/week) orally **(AI)**.[51] Approximately two-thirds of patients intolerant to TMP-SMX can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or aerosolized pentamidine but slightly less effective than TMP-SMX.[39,50]

Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and are old enough to use nebulization with a Respirgard II® nebulizer (Marquest; Englewood, CO) **(BI*)**.[33] The dosage for all ages is 300 mg once a month.[45] Adverse reactions in HIV-infected children include cough, sneezing, and bronchospasm.[52] Atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Pyrimethamine-sulfadoxine (Fansidar®) also is recognized as an effective prophylactic regimen in adults **(CIII)**.[53] Although this drug was effective in preventing PCP in Iranian orphanages in the 1960s, it has not been evaluated adequately in HIV-infected children.

Intravenous (IV) pentamidine can be considered in children older than age 2 years when other options are unavailable **(BII*)**.[54]

### *Discontinuing Primary Prophylaxis*

Studies of HIV-infected adults and children following immune reconstitution after receipt of cART demonstrate acceptably low risks for PCP after discontinuation of prophylaxis.[55-60] Data from the PACTG 1008 study evaluated 235 HIV-infected children and adolescents on antiretroviral therapy who received PCP prophylaxis for ≥6 months and achieved CD4 percentages ≥20% for patients aged >6 years and ≥25% for patients aged 2 to 6 years, after which the prophylaxis was stopped.[55] At median follow-up of 2.5 years (547 person-years), no cases of PCP occurred in children not receiving prophylaxis; 9.4% of patients enrolled required reinstitution of PCP prophylaxis because of low CD4 counts during the observation period. These data, along with data from studies in adults, support the expectation for very low risk for PCP after prophylaxis is discontinued in children who have achieved immune reconstitution.

Discontinuation of PCP prophylaxis should be considered for HIV-infected children when, after receiving cART for ≥6 months, CD4 percentage is ≥15% or CD4 count is ≥200 cells/mm$^3$ for patients aged ≥6 years **(BII)** and CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm$^3$ for patients aged 1 to <6 years **(BII)** for >3 consecutive months.[55,61]

Subsequently, the CD4 percentage and CD4 count should be reevaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached **(BIII)**. PCP prophylaxis should not be discontinued in HIV-infected infants aged <1 year.[62]

## Treatment Recommendations

### *Treating Disease*

TMP-SMX is the recommended treatment for PCP **(AI)**.[38,63,64] The dose for HIV-infected children aged >2 months is 3.75 to 5 mg/kg body weight/dose of the TMP component and 19 to 25 mg/kg body weight/dose of the SMX component administered IV every 6 hours, with each IV dose infused over 1 hour for 21 days **(AI)**.[62] 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)**.[62] Effective therapeutic serum concentrations of 5 to 10 µg/mL TMP can be reached with the recommended dose administered orally in HIV-infected children.[65]

IV pentamidine isethionate (4 mg/kg body weight) 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*)**.[62,66,67] No evidence exists for synergistic or additive effects on efficacy of these agents;[68] therefore, because of potential increased toxicity, their combined use is not recommended **(BIII)**.[62] In patients with clinical improvement after 7 to 10 days of IV therapy with pentamidine, an oral regimen (i.e., atovaquone [**BI**] or TMP/dapsone [**CIII**]) can be considered to complete a 21-day course.[62]

Atovaquone is an alternative for treatment of mild to moderately severe PCP in adults **(BI)**.[39,63,69] The dosage for adolescents aged ≥13 years is 750 mg/dose (5 mL) administered orally twice daily with food.[39,63,69-71] Therapeutic data are limited for children, but based on studies of prophylaxis, the primary dosage for children <3 months and >24 months to 12 years of age is 30 to 40 mg/kg body weight/dose administered orally once a day with food, and for children aged 2 to 24 months of age is a higher dose of 45 mg/kg body weight/dose once daily **(BI*)**.[49,50] Based on adult studies that use twice-daily dosing, some experts also use an alternate dosing regimen for children <3 months and >24 months to age 12 years of 15 to 20 mg/kg body weight/dose administered orally twice daily with food, and for children aged 2 to 24 months, a dose of 22.5 mg/kg body weight/dose twice daily with food **(CIII)**. Food increases the bioavailability of atovaquone approximately threefold compared with that achieved with the fasting state. Atovaquone concentration increases with co-administration of fluconazole and prednisone and decreases with co-administration of acyclovir, opiates, cephalosporins, rifampin, and benzodiazepines. Some experts suggest desensitizing the patient to allow for use of TMP-SMX.

Dapsone/TMP is effective in treating mild-to-moderate PCP in adults **(BI)**;[72] data on toxicity and efficacy among children are limited. The dosage of dapsone for adolescents and adults is 100 mg (total dose)/dose orally once daily and TMP 5 mg/kg body weight/dose three times per day administered for 21 days. In children aged <13 years, a dapsone dosage of 2 mg/kg body weight/dose once daily is required to achieve therapeutic levels **(AI)**.[73] The pediatric dose of TMP is 5 mg/kg body weight/day/dose three times per day. Dapsone is less effective than the combination.[74] Clindamycin/primaquine has been found to be effective in treating mild to moderate PCP in adults but can be considered as an alternative therapy for PCP in children despite lack of pediatric data. **(CIII)**. Primaquine is contraindicated in patients with glucose-6-dehydrogenase deficiency because of the possibility of inducing hemolytic anemia. Dosing information for treating PCP is available only for adults. For patients who weigh >60 kg, clindamycin 600 mg IV every 6 hours for 10 days, then 300 to 450 mg orally every 6 hours to complete 21 days of treatment, is recommended. Primaquine is administered as 30 mg of base orally for 21 days. Dosing for children is based on use of these drugs for treating other infections; the usual pediatric dose of clindamycin for treating bacterial infection is 10 mg/kg body weight/dose every 6 hours, and the pediatric dose of primaquine equivalent to an adult dose of 20 mg base (when used for malaria) is 0.3 mg/kg body weight/day of the base.

On the basis of studies in both adults[75-79] and children,[80] a short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis **(AI*)**. Pediatric studies have indicated reduced acute respiratory failure, decreased need for ventilation, and decreased mortality with early use of corticosteroids in HIV-infected children who have PCP.[80-82] Indications for corticosteroid treatment include a $PaO_2$ value of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. Doses for children vary between studies. A commonly used scheme is prednisone 1 mg/kg of body weight/dose twice daily on days 1 through 5; 0.5 mg/kg/dose twice daily on days 6 through 10; and 0.5 mg/kg of body weight/dose once daily on days 11 through 21. Alternative regimens include:

1. Adult dosage of prednisone: 40 mg/dose twice daily on days 1 through 5; 40 mg/dose once daily on days 6 through 10; 20 mg/dose once daily on days 11 through 21, and
2. Methylprednisolone IV 1 mg/kg/dose every 6 hours on days 1 through 7; 1 mg/kg/dose twice daily on days 8 through 9; 0.5 mg/kg/dose twice daily on days 10 and 11; and 1 mg/kg/dose once daily on days 12–16.

Some case reports have documented improved pulmonary function with use of surfactant in cases of severe disease such as respiratory distress syndrome with established respiratory failure requiring ventilation.[83-85] Alterations in surfactant function and composition have been demonstrated in HIV-infected adults with PCP.[86] Data are insufficient to recommend surfactant administration for PCP in children.

## *Monitoring and Adverse Events (Including IRIS)*

Clinical parameters for monitoring disease status include temperature, respiratory rate, arterial oxygen saturation, and chest radiograph.[87] Clinical improvement can be expected at a mean of approximately 4.5 ± 2.5 days and radiographic improvement at approximately 7.7 ± 4.5 days.[87]

Immune reconstitution inflammatory syndrome (IRIS) has been less frequently associated with *Pneumocystis* infection (2% of 44 adults with IRIS) than with several other OIs in HIV-infected adults and children.[88] Whether this low rate is related to PCP prophylaxis is unknown.

In children, adverse reactions to TMP-SMX include rash (mild maculopapular in most cases but rarely erythema multiforme and Stevens-Johnson syndrome [SJS]), hematologic abnormalities (e.g., neutropenia, thrombocytopenia, megaloblastic or aplastic anemia), GI complaints (usually mild), hepatitis, and renal disorders (e.g., interstitial nephritis).[89,90] Data from a PACTG study of HIV-infected children at high risk of

PCP receiving TMP-SMX for a median of 3 years showed 28% had a rash, 9.3% had neutropenia, 8.8% had thrombocytopenia, and 2.2% had anemia.[49] None were fatal or irreversible reactions. Some very mild reactions will resolve while the drug is continued. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. Based on adult randomized clinical trials, unless the reaction has been life-threatening, TMP-SMX prophylaxis can be resumed in children, preferably by beginning with low desensitizing daily doses and gradually increasing to therapeutic dosing **(CIII)**.[91,92] In adults, 75% of patients affected tolerated re-challenge with TMP-SMX.[92] The overall frequency of adverse reactions appears to be lower in HIV-infected children than in adults; approximately 15% of children have substantial adverse reactions to TMP-SMX.[57] If an urticarial rash or SJS occurs, TMP-SMX should be discontinued and not re-administered **(AIII)**.[89,90,92]

The most common adverse drug reaction to pentamidine isethionate is renal toxicity, which usually occurs after 2 weeks of therapy and can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval (torsades de pointes), and cardiac arrhythmias can occur. Hypoglycemia (usually after 5–7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus also have been reported. Patients may report a metallic or bitter taste. Serious adverse reactions to pentamidine have been reported in approximately 17% of children receiving the drug.[93] This drug should not be administered with other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) or with agents associated with pancreatitis (e.g., didanosine).

With dapsone and TMP, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemoglobinemia, anemia, and thrombocytopenia.[72,74] Dapsone is the problematic component of the combination and accounts for most of the adverse reactions.[50]

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

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

### *Managing Treatment Failure*

Occasionally an inflammatory reaction, thought to be due to antibiotic-induced killing of the organism in the lungs, can result in an initial early and reversible deterioration during the first 3 to 5 days of therapy, so an adequate trial of therapy is needed before switching drugs because of lack of clinical improvement. Clinical failure is defined by lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Other concomitant infections need to be excluded as causes of clinical failure. With evidence of treatment failure after the use of TMP-SMX, therapy can be changed. If tolerated, pentamidine isethionate is the drug of next choice **(AI*)**.[94,95] No evidence exists for synergistic or additive therapeutic effects; therefore, because of potential increased toxicity, their combination is not recommended.

### *Preventing Recurrence*

None of the drugs administered to treat and prevent PCP completely eliminates *Pneumocystis*, and prophylaxis is effective only while the selected drug is administered. Patients who have experienced an episode of PCP should remain on a prophylactic regimen after completion of treatment unless they meet criteria for discontinuing secondary prophylaxis **(AIII)**.[95]

### *Discontinuing Secondary Prophylaxis*

In most patients, secondary prophylaxis can be discontinued using the same criteria as for discontinuing primary prophylaxis. PCP prophylaxis is not to be discontinued in HIV-infected infants aged <1 year. 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 **(AIII)**.[96] If PCP recurs at a CD4 count ≥ 200 cells/mm$^3$, lifelong prophylaxis should be administered **(CIII)**.

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**Dosing Recommendations for Prevention and Treatment of Pneumocystis Pneumonia** (page 1 of 2)

<table>
<tr><th>Indication</th><th>First Choice</th><th>Alternative</th><th>Comments/Special Issues</th></tr>
<tr><td>Primary Prophylaxis</td><td>• TMP-SMX (Cotrimoxazole): TMP 2.5–5 mg/kg body weight/dose with SMX 12.5–25 mg/kg body weight/dose twice per day. Dosing based on TMP component.<br>• The total daily dose should not exceed 320 mg TMP and 1600 mg SMX. Several dosing schemes have been used successfully—<br>  • Given 3 days per week on consecutive days or on alternate days<br>  • Given 2 days per week on consecutive days or on alternate days<br>  • Given every day (total daily dose of TMP 5–10 mg/kg body weight given as a single dose each day)</td><td><u>Dapsone</u><br>Children aged ≥1 months:<br>• 2 mg/kg body weight (maximum 100 mg) by mouth once daily or 4 mg/kg body weight (maximum 200 mg) by mouth once weekly<br><u>Atovaquone</u><br>Children Aged 1–3 Months and >24 Months–12 Years:<br>• 30-40 mg/kg body weight/dose by mouth once daily with food<br>Children Aged 4–24 Months:<br>• 45 mg/kg body weight/dose by mouth once daily with food<br>Children Aged ≥13 Years:<br>• 1500 mg (10 cc oral yellow suspension) per dose by mouth once daily<br><u>Aerosolized Pentamidine</u><br>Children Aged ≥5 Years:<br>• 300 mg every month via Respirgard II™ nebulizer (manufactured by Marquest; Englewood, Colorado)</td><td><u>Primary Prophylaxis Indicated For</u>:<br>• All HIV-infected or HIV-indeterminate infants from aged 4–6 weeks to 12 months regardless of CD4 cell count/percentage<br>• HIV-infected children aged 1 to <6 years with CD4 count <500 cells/mm$^3$ or CD4 percentage <15%; HIV-infected children aged 6–12 years with CD4 count <200 cells/mm$^3$ or CD4 percentage <15%<br><u>Criteria for Discontinuing Primary Prophylaxis</u>:<br>Note: Do not discontinue in HIV-infected children aged <1 year<br>After ≥6 Months of cART:<br>• Aged 1 to <6 years; CD4 percentage ≥15% or CD4 count is ≥500 cells/mm$^3$ for >3 consecutive months, or<br>• Aged ≥6 years, CD4 percentage ≥15% or CD4 count is ≥200 cells/mm$^3$ for >3 consecutive months<br><u>Criteria for Restarting Primary Prophylaxis</u>:<br>• Aged 1 to < 6 years with CD4 percentage <15 or CD4 count <500 cells/mm$^3$<br>• Aged ≥6 years with CD4 percentage <15% or CD4 count <200 cells/mm$^3$</td></tr>
<tr><td>Secondary Prophylaxis<br>Prior PCP</td><td>Same as for primary prophylaxis.</td><td>Same as for primary prophylaxis.</td><td><u>Secondary Prophylaxis Indicated For</u>:<br>• Children with prior episode of PCP<br><u>Criteria for Discontinuing Secondary Prophylaxis</u>:<br>• Same as for primary prophylaxis<br><u>Criteria for Restarting Secondary Prophylaxis</u>:<br>• Same as for primary prophylaxis</td></tr>
</table>

**Dosing Recommendations for Prevention and Treatment of Pneumocystis Pneumonia** (page 2 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Treatment** | TMP-SMX 3.75–5 mg/kg body weight/dose TMP (based on TMP component) every 6 hours IV or orally given for 21 days (followed by secondary prophylaxis dosing) | If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy<br>*Pentamidine:*<br>• 4 mg/kg body weight/dose IV/IM once daily is the first choice alternative regimen. **Note:** Pentamidine can be changed to atovaquone after 7–10 days IV therapy.<br>*Atovaquone*<br>*Daily Dosing:*<br>• Children aged 1–3 months and >24 months–12 years: 30-40 mg/kg body weight/dose by mouth once daily with food<br>• Children aged 4–24 months: 45 mg/kg body weight/dose by mouth once daily with food<br>*Twice-Daily Dosing*:*<br>• Children aged ≥13 years: 750 mg/dose by mouth twice daily | After acute pneumonitis resolved in mild-moderate disease, IV TMP-SMX can be changed to oral. For oral administration, total daily dose of TMP-SMX can also be administered in 3 divided doses (every 8 hours).<br>Dapsone 2 mg/kg body weight by mouth once daily (maximum 100 mg/day) **plus** trimethoprim 5 mg/kg body weight by mouth every 8 hours has been used in adults but data in children are limited.<br>Primaquine base 0.3 mg/kg body weight by mouth once daily (maximum 30 mg/day) **plus** clindamycin 10 mg/kg body weight/dose IV or by mouth (maximum 600 mg given IV and 300–450 mg given orally) every 6 hours has been used in adults, but data in children are not available.<br>Indications for Corticosteroids:<br>• $PaO_2$ <70 mm Hg at room air or alveolar-arterial oxygen gradient >35 mm Hg<br>*Prednisone Dose:*<br>• 1 mg/kg body weight/dose by mouth twice daily for 5 days, then<br>• 0.5–1 mg/kg body weight/dose by mouth twice daily for 5 days, then<br>• 0.5 mg/kg body weight by mouth once daily for days 11 to 21.<br>Alternative Corticosteroid Regimens Include:<br>• Adult dosage of prednisone: 40 mg/dose twice daily on days 1–5, 40 mg/dose once daily on days 6–10, 20 mg/dose once daily on days 11–21, and<br>• Methylprednisolone IV 1 mg/kg/dose every 6 hours on days 1–7, 1 mg/kg/dose twice daily on days 8–9, 0.5 mg/kg/dose twice daily on days 10 and 11, and 1 mg/kg/dose once daily on days 12–16.<br>Chronic suppressive therapy (secondary prophylaxis) with TMP/SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis). |

*Some experts use twice-daily dosing of atovaquone as alternative treatment for PCP in children aged <12 years:

- Children aged 1–3 months and >24 months to 12 years: 15–20 mg/kg body weight/dose by mouth twice daily with food
- Children aged 4–24 months: 22.5 mg/kg body weight/dose by mouth twice daily with food.

**Key to Acronyms:** cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IM = intramuscular; IV = intravenous; PCP = *Pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole

**Note:** Information included in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for products or indications. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval.

# Syphilis

(Last updated: October 6, 2013; last reviewed: January 24, 2022)

| Panel's Recommendations |
|---|
| Congenital Syphilis<br>• Infants should be evaluated and treated per guidelines for congenital syphilis, given the following maternal factors:<br>  o Untreated or inadequately treated syphilis (including treatment with erythromycin or any other non-penicillin regimen)<br>  o Lack of documentation of having received treatment,<br>  o Receipt of treatment <30 days before delivery,<br>  o Treatment with penicillin but maternal nontreponemal antibody titer at delivery is fourfold higher than the pretreatment titer, or<br>  o Fourfold or greater increase in nontreponemal antibody titer suggesting relapse or reinfection (**AII**).<br>• **Note**: For comprehensive discussion and recommendations, see the Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines, 2010.<br>• Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G for 10 days (**AII**).<br>• If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous crystalline penicillin G should be increased per treatment guidelines (**AII**).<br>• An alternative to aqueous crystalline penicillin G is procaine penicillin G for 10 days (**BII**).<br>• 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**).<br>• 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**).<br>• 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**).<br>Sexually-Acquired Syphilis<br>*Early Syphilis*<br>• 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**).<br>• 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

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

## Epidemiology

*Treponema pallidum* can be transmitted from mother to child at any stage of pregnancy or during delivery. Among women with untreated primary, secondary, early latent (lacking clinical manifestations within first year after infection), or late latent (lacking clinical manifestations >1 year since infection) syphilis at delivery, approximately 30%, 60%, 40%, and 7% of infants, respectively, will be infected. Treatment of the mother for syphilis ≥30 days before delivery is required for effective *in utero* treatment.

Congenital syphilis has been reported despite adequate maternal treatment. Factors that contribute to treatment failure include maternal stage of syphilis (early stage, including primary, secondary, or early latent syphilis), advancing gestational age at treatment, higher nontreponemal titers at treatment and delivery, and short interval from treatment to delivery (<30 days).[1,2] Since 1991, rates of congenital syphilis have trended downward 92% to 8.5 cases per 100,000 live births in 2011.[3] The continuing decline in the rate of congenital syphilis probably reflects the substantially reduced rate of primary and secondary syphilis in women during the last decade.

Drug use during pregnancy, particularly cocaine use, has been associated with increased risk of maternal syphilis and congenital infection.[4] Similarly, HIV-infected women have a higher prevalence of untreated or inadequately treated syphilis during pregnancy, which places their newborns at higher risk of congenital syphilis.[5] Rates of mother-to-child HIV transmission may be higher when syphilis coinfection is present during pregnancy.[5-7] Risk of HIV transmission does not appear to be higher in mothers whose syphilis is effectively treated before pregnancy.[5]

Although individuals aged 15 to 24 represent one-quarter of the ever-sexually-active population aged 15 to 44, approximately half of sexually transmitted diseases (STDs) diagnosed annually in the United States occur in individuals aged 15 to 24 years.[8,9] Furthermore, individuals in this age group accounted for 28% of primary and secondary syphilis cases during 2011.[3] In 2011, the rate of primary and secondary syphilis was highest among individuals aged 20 to 24 years and 25 to 29 years (13.8 and 12.1 cases per 100,000 population, respectively). Nevertheless, the prevalence and incidence of syphilis in HIV-infected youth and of HIV infection in youth with syphilis are appreciable; in a study of 320 HIV-infected and HIV-uninfected U.S. adolescents aged 12 to 19 years, the prevalence of syphilis was 9% in HIV-infected girls and 6% in HIV-infected boys.[10] In a meta-analysis of 30 studies including individuals of all ages, the median HIV seroprevalence in those infected with syphilis in the United States was 15.7% (27.5% in men and 12.4% in women with syphilis).[11] In 2010, coinfection with HIV was reported in 46% of 15- to 29-year-old men who have sex with men with primary and secondary syphilis who knew their HIV status.[12]

## Clinical Manifestations

Untreated early syphilis during pregnancy can lead to spontaneous abortion, stillbirth, hydrops fetalis, preterm delivery, and perinatal death in up to 40% of pregnancies.[13] In children with congenital syphilis, two characteristic syndromes of clinical disease exist: early and late congenital syphilis. *Early congenital syphilis* refers to clinical manifestations that appear during the first 2 years of life. *Late congenital syphilis* refers to clinical manifestations that appear in children older than age 2 years.

At birth, infected infants may manifest signs such as hepatosplenomegaly, jaundice, mucocutaneous lesions (e.g., skin rash, nasal discharge, mucous patches, condyloma lata), lymphadenopathy, pseudoparalysis of an extremity, anemia, thrombocytopenia, pneumonia, and skeletal lesions (e.g., osteochondritis, periostitis, or osteitis). In a study of 148 infants born to mothers with untreated or inadequately treated syphilis, 47% had clinical, radiographic, or conventional laboratory findings consistent with congenital syphilis, and 44% had a positive rabbit infectivity test, polymerase chain reaction assay, or immunoglobulin M (IgM) immunoblot of serum, blood, or cerebrospinal fluid (CSF).[14] Manifestations of congenital syphilis in infants of HIV-infected women are expected to be similar to those in HIV-unexposed infants. However, as many as 60% of infants with congenital syphilis do not have any clinical signs at birth.[15] If untreated, these asymptomatic infants can develop clinically apparent disease in the ensuing 3 weeks to 6 months. In addition, fever, nephrotic syndrome, and hypopituitarism can occur. Clinical manifestations of late congenital syphilis are similar to late manifestations of syphilis in adults (e.g., involvement of bone and soft tissue, eyes, ears, and the central nervous system [CNS]).

The manifestations of sexually acquired syphilis in older children and adolescents are similar to those in adults (see Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults).[16] HIV-infected individuals with early syphilis may be at increased risk of neurologic complications and may have higher rates of serologic treatment failure.[17]

## Diagnosis

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

All infants born to women with reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal test (e.g., Venereal Disease Research Laboratory [VDRL] slide test, rapid plasma reagin [RPR], the automated reagin test) from the infant and compared with the same test done at the same laboratory on the mother's serum. Umbilical cord specimens should not be tested because of the potential for maternal blood contamination. Specific treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and *T. pallidum* particle agglutination (TP-PA) test, are not necessary to evaluate congenital syphilis in the neonate. There is no commercially available IgM test recommended for diagnostic use. **Note**: Some laboratories use treponemal tests (e.g., enzyme immunoassay, chemiluminescence) for initial screening, and nontreponemal tests for confirmation of positive specimens.[18] However, such an approach with congenital syphilis has not been published.

Congenital syphilis can be definitively diagnosed if *T. pallidum* is detected by using darkfield microscopic examination or special stains of lesions or body fluids such as umbilical cord, placenta, nasal discharge, or skin lesion material from an infant. Failure to detect *T. pallidum* does not definitively rule out infection because false-negative results are common.[19] A quantitative nontreponemal serologic titer in an infant that is fourfold higher than the mother's is suggestive of infection. Infection also should be assumed in infants born to mothers who were untreated or inadequately treated for syphilis prior to delivery (e.g., non-penicillin regimen or treatment completion <30 days before delivery), regardless of lack of physical, radiographic, or laboratory findings in the infants suggestive of congenital syphilis.

Evaluation of suspected cases of congenital syphilis should include a careful and complete physical examination. Physical signs and symptoms of congenital syphilis include, but are not limited to, non-immune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseudoparalysis of an extremity. Further evaluation to support a diagnosis of congenital syphilis depends on maternal treatment history for syphilis, findings on physical examination, and planned infant treatment. and may include a complete blood count and differential and platelet count, long bone radiographs, and CSF analysis for VDRL, cell count, and protein. A positive CSF VDRL test, elevated CSF protein, and/or elevated CSF white blood cell (WBC) count without other causes may be due to congenital syphilis. Other tests should be performed as clinically indicated (e.g., chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, auditory brainstem response). Individuals with latent syphilis who have neurologic or ophthalmologic signs or symptoms, active tertiary syphilis, or serologic treatment failure should have a CSF examination. Different scenarios indicating clinical management and follow-up recommendations for congenital syphilis are provided on page 36 through 37 of the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010.

For diagnosis of acquired syphilis, a reactive nontreponemal test must be confirmed by a specific treponemal test such as FTA-ABS or TP-PA. Treponemal tests usually remain positive for life, even with successful treatment. The prozone phenomenon (a weakly reactive or falsely negative) reaction is more common in HIV-infected patients.[20] Treponemal antibody titers do not correlate with disease activity and should not be used to monitor treatment response.

## Prevention Recommendations

### *Preventing Exposure*

#### Congenital Syphilis

Effective identification and treatment of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk of congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as part of management of pregnant women who have syphilis, information about treatment of sex partners should be obtained to assess the risk of reinfection. Serologic testing at delivery of the mother's serum is preferred over testing of the infant's serum because the serologic tests performed on infant serum can be non-reactive if the mother's serologic test result is of low titer or the mother was infected late in pregnancy. No HIV-exposed infant should leave the hospital unless the maternal syphilis serologic status has been documented at least once during pregnancy and at delivery in communities and populations in which the risk of congenital syphilis is high.[21,22] Routine screening of serum from newborns or umbilical cord blood is not recommended.

**Acquired Syphilis**

Primary prevention of syphilis includes routine discussion of sexual behaviors that may place individuals at risk of infection. Providers should discuss risk reduction messages that are client-centered and provide specific actions that can reduce the risk of STD acquisition and HIV transmission.[23-25]

Routine serologic screening for syphilis is recommended at least annually for all sexually active HIV-infected individuals, with more frequent screening (i.e., 3–6 months) depending on individual risk behaviors (e.g., as multiple partners, sex in conjunction with illicit drug use, methamphetamine use, partners who participate in such activities).[17,26] Syphilis in an HIV-infected individual indicates high-risk behavior and should prompt intensified counseling messages and consideration of referral for behavioral intervention. Patients undergoing screening or treatment for syphilis also should be evaluated for other STDs.[27]

## *Discontinuing Primary Prophylaxis*

Not applicable.

# Treatment Recommendations

## *Treating Disease*

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

**Congenital Syphilis**

Data are insufficient to determine whether infants who have congenital syphilis and whose mothers are coinfected with HIV require different evaluation, therapy, or follow-up for syphilis than that recommended for infants born to mothers who are not HIV-coinfected. Response to standard treatment may differ in HIV-infected mothers. For example, some studies in adults have shown a lag in serologic improvement in appropriately treated HIV-infected patients.[28,29]

Treatment for congenital syphilis should be administered to infants whose mothers:

- Have been untreated or inadequately treated for syphilis (including treatment with erythromycin or any other non-penicillin regimen),
- Have no documentation of receiving treatment,
- Received treatment <30 days before delivery, or
- Have experienced a fourfold or greater increase in nontreponemal antibody titer suggestive of relapse or reinfection (**AII**) (proven or highly probable disease). (Sexually Transmitted Disease Treatment Guidelines, 2010)[27]

Infants should be treated regardless of maternal treatment history if they have an abnormal physical examination consistent with congenital syphilis, positive darkfield or fluorescent antibody test of body fluid(s), or serum quantitative nontreponemal serologic titer that is at least fourfold greater than maternal titer (**AII**) (proven or highly probable disease).[27]

Treatment for proven or highly probable congenital syphilis is aqueous crystalline penicillin G 100,000 to 150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose intravenously (IV) every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days (**AII**). If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous penicillin G should be increased to 200,000 to 300,000 units/kg/day IV, administered as 50,000 units/kg body weight/dose IV every 4 to 6 hours for 10 days (**AII**). If 1 day of therapy is missed, the entire course should be restarted. An alternative to aqueous penicillin G is procaine penicillin G 50,000 units/kg body weight/dose intramuscularly (IM) in a single dose daily for 10 days (**BII**). However, aqueous penicillin G is preferred because of its higher penetration into the CSF. Insufficient data are available on the effectiveness of ampicillin or other therapies for treatment of congenital syphilis.

For infants who do not meet criteria for proven or highly probable disease, treatment options are influenced by several factors, including maternal treatment, maternal serologic results, and response to therapy, and infant physical exam, infant serologic results, and other laboratory test results. Scenarios that include variations of these factors with treatment recommendations are provided in detail in on pages 36 and 37 of the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010.[27] In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable.

### Acquired Syphilis

Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G 50,000 units/kg body weight IM (up to the adult dose of 2.4 million units) for early-stage disease (i.e., primary, secondary, and early latent disease) (**AII**). For late latent disease, three doses of benzathine penicillin G 50,000 units/kg body weight (up to the adult dose of 2.4 million units) should be administered IM once weekly for 3 doses (total 150,000 units/kg body weight, up to the adult total dose of 7.2 million units) (**AIII**). Alternative therapies (e.g., ceftriaxone, azithromycin) should be administered to HIV-infected patients only when treatment with penicillin is not feasible, and with close clinical and serologic monitoring because data on their use are limited (**BII**). See the Sexually Transmitted Disease Treatment Guidelines, 2010.[27] Neurosyphilis should be treated with aqueous penicillin G 200,000 to 300,000 units/kg body weight per day admistered as 50,000 units/kg body weight per dose IV every 4 to 6 hours (maximum dosage: 18–24 million units/day) for 10 to 14 days (**AII**).[30] See *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults* for dosing recommendations for older HIV-infected adolescents with acquired syphilis.[16]

## *Monitoring and Adverse Events (Including IRIS)*

All infants with a reactive nontreponemal test for syphilis (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2 to 3 months until the test becomes non-reactive or the titer has decreased fourfold (**AIII**). Nontreponemal antibody titers should decline by age 3 months and should be non-reactive by age 6 months in infants who were not infected (i.e., if the reactive test result was caused by passive transfer of maternal IgG antibody) or who were infected but have been adequately treated. The serologic response after therapy may be slower in infants treated after the neonatal period. Whether children with congenital syphilis who also are HIV-infected take longer to become nonreactive and require retreatment is unknown.

Treponemal tests should not be used to evaluate treatment response because in infected children, the results can remain positive despite effective therapy or be related to maternal infection. Passively transferred maternal treponemal antibodies can be present in infants until age 15 months. A reactive treponemal test after age 18 months is diagnostic of congenital syphilis. If the nontreponemal test is non-reactive at that time, no further evaluation or treatment is necessary. Infants in whom the nontreponemal test is reactive at age 18 months should be fully (re)evaluated and (re)treated for congenital syphilis (**AIII**).

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

HIV-infected children and adolescents with acquired primary and secondary syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy (**AIII**); nontreponemal test titers should decline by at least fourfold by 6 to 12 months after successful therapy, with examination of CSF and re-treatment strongly considered in the absence of such decline. For acquired syphilis of longer duration (e.g., early and late latent syphilis), follow up is indicated at 6, 12,18, and 24 months; fourfold decline should be expected by 12 to 24 months. If initial CSF examination demonstrated pleocytosis, repeat lumbar puncture should be conducted at 6 months after therapy, and then every 6 months until the cell count is normal (**AIII**). Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein levels after therapy, but changes in these parameters occur more slowly than changes in CSF cell counts. Data from HIV-infected adults with neurosyphilis suggest that CSF abnormalities may persist for extended times, and close clinical follow up is warranted.[31]

Syphilis in HIV-infected children (congenital or acquired) manifesting as immune response inflammatory syndrome (IRIS) has not been reported, and only very rare reports of syphilis-associated IRIS in adults (primarily syphilitic ocular inflammatory disease) have been reported.[32,33]

## *Managing Treatment Failure*

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

Management of failed treatment of acquired syphilis in older children and adolescents is identical to that in adults.[17] Re-treatment of patients with primary or secondary syphilis should be considered 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 (**BIII**).

Adolescents or adults in whom CSF examination does not confirm a neurosyphilis diagnosis should receive benzathine penicillin G 2.4 million units IM, at 1-week intervals for 3 weeks (**BIII**). If titers fail to respond appropriately after re-treatment, the value of repeat CSF evaluation or re-treatment is unclear, but not recommended.

Re-treatment is warranted for patients with early or late-latent syphilis who have new or sustained clinical signs or symptoms of syphilis, have a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (less than fourfold decline in nontreponemal test titer) within 12 to 24 months after therapy **if initial titer was high (>1:32)** (**BIII**). Repeat CSF examination should be performed on these patients, and if the results are consistent with CNS involvement, re-treatment should follow the neurosyphilis recommendations (**AIII**). Adolescents or adults whose CSF profile is not indicative of CNS disease should receive a repeat course of benzathine penicillin 2.4 million units IM weekly for 3 weeks (**BIII**); re-treatment of neurosyphilis should be considered in patients whose CSF WBC count has not decreased 6 months after completion of treatment or in whom CSF WBC count or protein is not normal after 2 years (**BIII**).

## *Preventing Recurrence*

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

## *Discontinuing Secondary Prophylaxis*

Not applicable.

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## Dosing Recommendations for Prevention and Treatment of Syphilis

| Preventive Regimen | | | |
|---|---|---|---|
| **Indication** | **First Choice** | **Alternative** | **Comments/Special Issues** |
| Primary Prophylaxis | N/A | N/A | Primary Prophylaxis Indicated for:<br>• N/A<br>Criteria for Discontinuing Primary Prophylaxis:<br>• N/A<br>Criteria for Restarting Primary Prophylaxis:<br>• N/A |
| Secondary Prophylaxis | N/A | N/A | Secondary Prophylaxis Indicated:<br>• N/A<br>Criteria For Discontinuing Secondary Prophylaxis:<br>• N/A<br>Criteria For Restarting Secondary Prophylaxis:<br>• N/A |
| Treatment | Congenital<br>*Proven or Highly Probable Disease*:<br>• Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 12 hours for the first 7 days of life, and then every 8 hours for 10 days<br>• If diagnosed after 1 month of age, aqueous penicillin G 200,000–300,000 unit/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10 days<br>*Possible Disease*:<br>• Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, | Congenital<br>*Proven or Highly Probable Disease (Less Desirable if CNS Involvement):*<br>• Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days<br>*Possible Disease*:<br>• Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010. | For treatment of congenital syphilis, repeat the entire course of treatment if >1 day of treatment is missed.<br>Examinations and serologic testing for children with congenital syphilis should occur every 2–3 months until the test becomes non-reactive or there is a fourfold decrease in titer. Children with increasing titers or persistently positive titers (even if low levels) at ages 6–12 months should be evaluated and considered for re-treatment.<br>In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable.<br>Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy. |

| Preventive Regimen | | | |
|---|---|---|---|
| Indication | First Choice | Alternative | Comments/Special Issues |
| | and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010.<br>Acquired<br>*Early Stage (Primary, Secondary, Early Latent)*:<br>• Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM for 1 dose<br>*Late Latent*<br>• Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM once weekly for 3 doses<br>*Neurosyphilis (Including Ocular)*:<br>• Aqueous penicillin G 200,000–300,000 units/kg body weight per day administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10–14 days | | |

Key: CDC = Centers for Disease Control and Prevention; IM = intramuscular; IV = intravenous; STD = sexually transmitted disease

# 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/mm$^3$ 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) **(AII*)**.
- Primary preventive therapy can be discontinued once a child responds to combination antiretroviral therapy (cART) with a sustained rise in CD4 percentage above 15% for children <6 years of age, and >200 cells/mm$^3$ for children aged ≥6 years **(BIII)**
- Most experts recommend treating pregnant women with acute toxoplasmosis in an attempt to prevent fetal infection **(BII)**. For more extensive information on diagnosis, prevention, and treatment of pregnant women with toxoplasmosis, please see the *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*.
- Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary Toxoplasma infection during pregnancy, regardless of whether treatment was administered during pregnancy **(BIII)**.
- The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin **(AII)**.
- The recommended duration of treatment of congenital toxoplasmosis in HIV-infected infants is 12 months **(AIII)**.
- Therapy for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin **(AI*)**. 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*

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

## Epidemiology

The major mode of transmission of *Toxoplasma gondii* infection to infants and young children is congenital, occurring almost exclusively in neonates born to women who sustain primary *Toxoplasma* infection during pregnancy. The estimated incidence of congenital toxoplasmosis in the United States is one case per 1,000 to 12,000 live-born infants.[1,2] The seroprevalence of *T. gondii* in U.S.-born individuals aged 12 to 49 years declined from 14.1% in the National Health and Nutrition Examination Survey from 1988 to 1994 to 9.0% from 1999 to 2004.[3] Older children, adolescents, and adults typically acquire *Toxoplasma* infection by eating undercooked meat that contains parasitic cysts or by unintentionally ingesting sporulated oocysts from cat feces in soil or contaminated food or water.[4] In the United States, eating raw shellfish including oysters, clams, and mussels was recently identified as a novel risk factor for acute infection.[5] Cats are the only definitive host for *T. gondii*. However, cats excrete oocysts in their feces only transiently after initial infection, and most studies have failed to show a correlation between cat ownership and *Toxoplasma* infection in humans. Indeed, *Toxoplasma* infection in humans in the United States has declined despite increased cat ownership.[4]

The overall risk of maternal-fetal transmission in HIV-uninfected women who acquire primary *Toxoplasma* infection during pregnancy is 29% (95% confidence interval [CI], 25%–33%), with variation depending upon the trimester during which primary maternal infection occurs.[6] The risk of congenital infection is low among infants born to women who become infected during the first trimester (range: 2%–6%) but increases sharply thereafter, with a risk as high as 81% in women who become infected during the last few weeks of pregnancy.[6,7] Infection of the fetus in early gestation usually results in more severe disease than does infection late in gestation.

The prevalence of latent *Toxoplasma* infection in HIV-infected and HIV–uninfected women in the United States was assessed in a cross-sectional study of 2,525 non-pregnant women enrolled in the Women's Interagency Health Study.[8] The prevalence of *Toxoplasma* seropositivity was 15% and did not differ by HIV infection status. The overall rate of mother-to-child transmission (MTCT) of *Toxoplasma* in HIV-infected pregnant women is unknown; however, a few cases of MTCT of *Toxoplasma* in HIV-infected women have been reported.[9-13] HIV-infected women may be at increased risk of transmitting *T. gondii* to their fetuses, and serologic testing for *Toxoplasma* should be performed on all HIV-infected pregnant women. Prenatal transmission of *T. gondii* is rare from women without HIV infection who acquired chronic *Toxoplasma* infection before pregnancy.[14] However, with HIV coinfection, perinatal transmission of *Toxoplasma* has been observed in women with chronic *Toxoplasma* infection (transmission rate: <4%), presumably because of reactivation of replication of the organism in women who are severely immunosuppressed.[9-12]

Central nervous system (CNS) infection with *T. gondii* was reported as an AIDS-indicator condition in <1% of pediatric AIDS cases before the advent of combination antiretroviral therapy (cART).[15] Since then, this condition is rarely encountered in HIV-infected U.S. children. CNS toxoplasmosis occurred in 5 of 2,767 (0.2%) HIV-infected children enrolled in the long-term follow-up study Pediatric AIDS Clinical Trials Group 219c since cART has been available.[16] Infection is considered to have occurred *in utero* in most cases of *Toxoplasma* encephalitis (TE) seen in HIV-infected children.

More rarely, it has been reported in older HIV-infected children, who presumably had primary acquired toxoplasmosis.[17-19] As in adults, the greatest risk is among severely immunosuppressed children (i.e., CD4 T lymphocyte [CD4] cell count <50 cells/mm$^3$).

## Clinical Manifestations

In studies of non-immunocompromised infants with congenital toxoplasmosis, most infants (70%–90%) are asymptomatic at birth. However, most asymptomatic children develop late sequelae (i.e., retinitis, visual impairment, and intellectual or neurologic impairment), with onset of symptoms ranging from several months to years after birth. Symptoms in newborns take either of two presentations: generalized disease or predominantly neurologic disease. Symptoms can include maculopapular rash; generalized lymphadenopathy; hepatosplenomegaly; jaundice; hematologic abnormalities including anemia, thrombocytopenia, and neutropenia; and substantial CNS disease including hydrocephalus, intracerebral calcification, microcephaly, chorioretinitis, and seizures.[20]

Toxoplasmosis acquired after birth most often is initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly.[21]

TE should be considered in all HIV-infected children with new neurologic findings, but especially those with severe immunosuppression. Although focal findings are typical, the initial presentation can vary and reflect diffuse CNS disease. Generalized symptoms include fever, reduced alertness, and seizures.

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

Less frequent presentations in HIV-infected children with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis.[12,22]

## Diagnosis

All infants whose mothers are both HIV-infected and seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis **(AIII)**.[23] Congenital toxoplasmosis can be diagnosed by enzyme-linked immunoassay or an immunosorbent assay to detect *Toxoplasma*-specific immunoglobulin M (IgM), IgA, or IgE in neonatal serum within the first 6 months of life or persistence of specific immunoglobulin G antibody beyond age 12 months.[24-28] IgA may be more sensitive for detecting congenital infection than IgM or IgE.[25] However, approximately 20% to 30% of infants with congenital toxoplasmosis will not be identified during the neonatal period with IgA or IgM assays.[26]

Serologic testing is the major method of diagnosis, but interpretation of assays often is confusing and difficult. When considering a diagnosis of congenital toxoplasmosis, specialized reference laboratories can perform serology, isolation of organisms and polymerase chain reaction (PCR) and can offer assistance in interpreting results.[25,28]

Additional methods that can be used to diagnose infection in the newborn include isolation of the *Toxoplasma* parasite by mouse inoculation or inoculation in tissue cultures of cerebrospinal fluid (CSF), urine, placental tissue, amniotic fluid, or infant blood. *T. gondii* DNA can be detected by PCR performed on clinical specimens (e.g., white blood cells, CSF, amniotic fluid, tissue) in a reference laboratory.[25,26] The following evaluation should be undertaken for all newborns in whom a diagnosis of toxoplasmosis is suspected: ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and imaging of the head (either CT or magnetic resonance imaging [MRI] scans) to determine whether hydrocephalus or calcifications are present.

CNS toxoplasmosis is presumptively diagnosed on the basis of clinical symptoms, serologic evidence of infection, and presence of a space-occupying lesion on imaging studies of the brain.[29] TE rarely has been reported in individuals without *Toxoplasma*-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis. Brain computer tomography (CT) that demonstrates multiple, bilateral, ring-enhancing lesions, especially in the basal ganglia and cerebral corticomedullary junction, would be typical of TE. Calcifications are more typical in congenital toxoplasmosis than in TE seen later in life. Magnetic resonance imaging (MRI) is more sensitive and will confirm basal ganglia lesions in most patients.[30] F-fluoro-2-deoxyglucose–positive emission tomography reportedly is helpful in adults in distinguishing *Toxoplasma* abscesses from primary CNS lymphoma, but the accuracy is not high, and this test is not widely available.

Definitive diagnosis of TE requires histologic or cytologic confirmation by brain biopsy, which may demonstrate leptomeningeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Brain biopsy is reserved by some experts for patients who do not respond to specific therapy.

## Prevention Recommendations

### *Preventing Exposure*

All HIV-infected children and adolescents and their caregivers should be counseled about sources of *T. gondii* infection. They should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison **(BIII)**. All meat (lamb, beef, and pork) should be cooked to an internal temperature of 145°F for 3 minutes.[31] However, a study has found that *T. gondii* can survive at 64°C (147.2°F) for 3 minutes, so higher temperatures than this seem best for immunosuppressed patients.[32] Ground meat and wild game meat should be cooked to 71°C (160°F). Poultry should be cooked to 74°C (165°F). Hands should be washed after contact with raw meat and after gardening or other contact with soil; in addition, fruits and vegetables should be washed well before being eaten raw **(BIII)**. Stray cats should not be handled or adopted; a cat already in the household should be kept inside and the litter box changed daily, preferably by an HIV-uninfected individual who is not pregnant **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis **(AII)**.

## *Preventing Disease*

In the United States, routine *Toxoplasma* serologic screening of HIV-infected children whose mothers do not have toxoplasmosis is not recommended because of its low incidence. However, in regions with high incidence of *Toxoplasma* infection (≥1% per year), or for children immigrating from such regions, serologic testing can be selectively considered for HIV-infected children aged >12 months **(CIII)**. HIV-infected adolescents without previous *Toxoplasma* infection should undergo serologic testing **(CIII)**. *Toxoplasma*-seronegative adults and adolescents who are not taking *Pneumocystis* pneumonia (PCP) prophylaxis known to be active against TE should be retested for IgG antibody to *Toxoplasma* if their CD4 cell counts decline to <100 cells/mm$^3$ to determine whether they have seroconverted to *Toxoplasma*.

*Toxoplasma*-seropositive adolescents and adults who have CD4 cell counts <100 cells/mm$^3$ should be given prophylaxis against TE.[33] Specific levels of immunosuppression that increase the risk of TE in children are less well defined. *Toxoplasma*-seropositive children with CD4 percentages <15% should be given prophylaxis against TE **(AIII)**. For children aged ≥6 years, the same absolute CD4 count level used for HIV-infected adults can be used **(AIII)**.

In HIV-infected adolescents and adults, the double-strength-tablet daily dose of trimethoprim-sulfamethoxazole (TMP-SMX) recommended as the preferred regimen for PCP prophylaxis is effective TE prophylaxis **(AII)**.[33] Data from case series in children and from trials in adults support this as the preferred regimen in children using age-based dosing (See Table: Dosing Recommendations for the Prevention and Treatment of *Toxoplasma gondii*) **(BIII)**. TMP-SMX, one double-strength tablet 3 times weekly (or 3 consecutive days a week), is an alternative **(BIII)**. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which also is effective against PCP **(BI*)**.[34,35] Atovaquone with or without pyrimethamine also can be considered **(CIII)**. Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended **(AIII)**. Aerosolized pentamidine does not protect against TE and is not recommended.[33,36] Severely immunosuppressed children who are not receiving TMP-SMX or atovaquone who are seropositive for *Toxoplasma* should be given prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine) **(BIII)**.

## *Discontinuing Primary Prophylaxis*

Multiple observational studies[37-39] and two randomized trials[40,41] have reported that primary prophylaxis can be discontinued with minimal risk of TE in patients who have responded to cART with an increase in CD4 cell count to ≥200 cells/mm$^3$ for >6 months. Although patients with CD4 cell counts of <100 cells/mm$^3$ are at greatest risk of TE, the risk of TE when CD4 cell counts increase to 100 to 200 cells/mm$^3$ has not been studied as rigorously as an increase to >200 cells/mm$^3$. Thus, the recommendation for adults and adolescents specifies discontinuing prophylaxis after an increase to >200 cells/mm$^3$. Discontinuing primary TE prophylaxis when CD4 cell counts have increased to >200 cells/mm$^3$ is recommended because prophylaxis adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Data do not exist on the safety of discontinuing primary TE prophylaxis for HIV-infected children whose immunologic status improves on cART.

Data on adults suggest discontinuation of TMP-SMX may be safe once a child responds to cART with a sustained rise in CD4 percentage above 15%; for children aged ≥6 years, the same CD4 cell count used for HIV-infected adults can be used **(BIII)**. A sustained response in children has been defined as a CD4 count or percentage above the threshold level for >3 consecutive months after receiving cART for >6 months.

Prophylaxis should be reintroduced in HIV-infected adults **(AIII)**, adolescents **(AIII)**, and children ≥6 years old **(BIII)** if the CD4 cell count decreases to <100 to 200 cells/mm$^3$ or the CD4 percentage falls below 15% for HIV-infected children aged <6 years **(BIII)**.

## Treatment Recommendations

### *Treating Disease*

Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate infectious disease specialist. Although controversy exists about the efficacy of treating pregnant women who have acute toxoplasmosis in an attempt to prevent infection of the fetus,[42] most experts would recommend such therapy **(BII)**.[23] 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 (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII)**.[20,43] The preferred treatment 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 age-appropriate-dosed trimethoprim-sulfamethoxazole in place of the combination of sulfadiazine, pyrimethamine, and leucovorin. Although the optimal duration of therapy is undefined, the recommended duration of treatment for congenital toxoplasmosis in HIV-uninfected infants is 12 months **(AII)**.[43] Older HIV-infected children with acquired CNS, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(AI*)**. Acute therapy should be continued for 6 weeks, assuming clinical and radiologic improvement **(BII*)**. Longer courses of treatment may be required for extensive disease or poor response after 6 weeks. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin **(AI*)**. Azithromycin instead of clindamycin also has been used with pyrimethamine and leucovorin in sulfa-allergic adults, but this regimen has not been studied in children. Extrapolation of doses used in adults corresponds to a dose of 20 mg/kg given every 24 hours (maximum 1,000 mg) but this dose has not been evaluated in children.

Another alternative in adults is atovaquone plus pyrimethamine and leucovorin, or atovaquone with sulfadiazine alone, or atovaquone as a single agent in patients intolerant to both pyrimethamine and sulfadiazine; however, these regimens have not been studied in children **(BII*)**. In adults, atovaquone is dosed at twice the total daily dose used for PCP prophylaxis and is divided into four doses per day, but such dosing for treatment of acquired toxoplasmosis in children has not been evaluated. In a small (77 subjects) randomized trial in adults, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.[44] Others have reported similar efficacy in open-label observational studies.[45] However, this has not yet been studied in children.

For isolated ocular toxoplasmosis in immunocompetent hosts, TMP-SMX alone is as effective as pyrimethamine-sulfadiazine.[46] However, these data have not been duplicated in HIV-infected patients; therefore, this regimen cannot be recommended for this group of patients.

Based upon treatment of congenital toxoplasmosis in HIV-uninfected children, corticosteroids such as dexamethasone and prednisone are recommended for all HIV-infected children with CNS disease when CSF protein is highly elevated (i.e., >1,000 mg/dL) or who have focal lesions with substantial mass effects **(BIII)**.

Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible.

Anticonvulsants should be given to children with TE who have a history of seizures **(AIII)** but should not be administered prophylactically to children without a history of seizures **(BIII)**. Anticonvulsants, if administered, should be continued at least through acute therapy.

Although the initiation of cART aids in the treatment of many opportunistic infections and malignancies, it has not been definitively shown to improve the outcome of TE therapy.

## *Monitoring and Adverse Events, Including IRIS*

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

Toxoplasmosis-associated immune reconstitution inflammatory syndrome (IRIS) has been described rarely in HIV-infected adults and has not been described in HIV-infected children, although it could presumably occur.[47,48] IRIS in HIV-infected pregnant women may pose additional risk to the fetuses[49] although any unique risk for pregnant women co-infected with HIV and *Toxoplasma* has not been defined.

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

Adverse effects of sulfadiazine include rash, fever, leukopenia, hepatitis, gastrointestinal (GI) symptoms (e.g., nausea, vomiting, diarrhea), and crystalluria. Clindamycin can be associated with fever, rash, and GI symptoms (e.g., nausea; vomiting, and diarrhea, and including pseudomembranous colitis) and hepatotoxicity.

Drug interactions between anticonvulsant and antiretroviral drugs should be evaluated. Patients receiving corticosteroids should be closely monitored for development of other opportunistic infections.

## *Managing Treatment Failure*

Brain biopsy should be considered in the event of early clinical or radiologic neurologic deterioration despite adequate empiric treatment or in children who do not clinically respond to anti-*Toxoplasma* therapy after 10 to 14 days. In children who undergo brain biopsy and have confirmed histopathologic evidence of TE despite treatment, a switch to an alternative regimen as previously described should be considered **(BIII)**.

## *Preventing Recurrence*

Patients who have completed initial therapy for acquired TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI*)**[50,51] until immune reconstitution occurs with cART. The combination of pyrimethamine, sulfadiazine, and leucovorin is highly effective for this purpose **(AI*)**. A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin with leucovorin **(BI*)**; however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well. Data on adults indicate atovaquone with or without pyrimethamine also can be considered for children **(CIII)**. Limited data support the use of TMP-SMX for secondary prophylaxis;[52] this regimen should be used only for patients who do not tolerate pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CIII)** or if pyrimethamine is unavailable.

## *Discontinuing Secondary Prophylaxis*

Adults and adolescents receiving secondary prophylaxis for acquired TE are at low risk of recurrence of TE when they have successfully completed their initial therapy, continue to have no signs or symptoms of TE, and have a sustained increase in CD4 cell count of >200 cells/mm$^3$ after cART (i.e., >6 months).[38,39,41,53,54] Discontinuing chronic maintenance therapy in HIV-infected adolescents and adults who meet these criteria is a reasonable consideration. The highest risk of relapse appears to occur within the first 6 months after stopping secondary prophylaxis. Some specialists would obtain an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate. The safety of discontinuing secondary prophylaxis after immune reconstitution with cART in children has not been studied extensively. However, given the data in adults, clinicians caring for HIV-infected children aged 1 to <6 years can consider discontinuing secondary prophylaxis against *T. gondii* after they have completed TE therapy and ≥6 months of stable cART and are asymptomatic and once the CD4 percentage has risen to ≥15% for >6 consecutive months **(BIII)**. For children aged ≥6 years, the same CD4 cell count used in adults (CD4 count >200 cells/mm$^3$) also can be used **(BIII)**. Prophylaxis should be re-instituted if these parameters are not met.

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## Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis (page 1 of 3)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Primary Prophylaxis** | TMP-SMX 150/750 mg/$m^2$ body surface area once daily by mouth | For Children Aged ≥1 Month:<br>• Dapsone 2 mg/kg body weight or 15 mg/$m^2$ body surface area (maximum 25 mg) by mouth once daily, **plus**<br>• Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, **plus**<br>• Leucovorin 5 mg by mouth every 3 days<br>For Children Aged 1–3 Months and >24 Months:<br>• Atovaquone 30 mg/kg body weight by mouth once daily<br>Children Aged 4–24 Months:<br>• Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/$m^2$ body surface area (maximum 25 mg) by mouth once daily, **plus**<br>• Leucovorin 5 mg by mouth every 3 days<br>Acceptable Alternative Dosage Schedules for TMP-SMX:<br>• TMP-SMX 150/750 mg/$m^2$ body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week<br>• TMP-SMX 75/375 mg/$m^2$ body surface area per dose twice daily by mouth every day<br>• TMP-SMX 75/375 mg/$m^2$ body surface area per dose twice daily by mouth 3 times weekly on alternate days | Primary Prophylaxis Indicated For:<br>*IgG Antibody to Toxoplasma and Severe Immunosuppression:*<br>• HIV-infected children aged <6 years with CD4 percentage <15%; HIV-infected children aged ≥6 years with CD4 count <100 cells/$mm^3$<br>Criteria for Discontinuing Primary Prophylaxis:<br>**Note:** Do not discontinue in children aged <1 year<br>• After ≥6 months of cART, **and**<br>• Aged 1 to <6 years; CD4 percentage is ≥15% for >3 consecutive months<br>• Aged ≥6 years; CD4 count >200 cells/$mm^3$ for >3 consecutive months<br>Criteria for Restarting Primary Prophylaxis:<br>• Aged 1 to <6 years with CD4 percentage <15%<br>• Aged ≥6 years with CD4 count <100 to 200 cells/$mm^3$ |
| **Secondary Prophylaxis** (Suppressive Therapy) | • Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, **plus**<br>• Pyrimethamine 1 mg/kg body weight or 15 mg/$m^2$ body surface area (maximum 25 mg) by mouth once daily, **plus**<br>• Leucovorin 5 mg by mouth once every 3 days | • Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, **plus**<br>• Pyrimethamine 1 mg/kg body weight or 15 mg/$m^2$ body surface area (maximum 25 mg) by mouth once daily, plus<br>• Leucovorin 5 mg by mouth once every 3 days<br>Children Aged 1–3 Months and >24 Months:<br>• Atovaquone 30 mg/kg body weight by mouth once daily<br>• Leucovorin, 5 mg by mouth every 3 days<br>• TMP-SMX, 150/750 mg/$m^2$ body surface area once daily by mouth | Secondary Prophylaxis Indicated:<br>• Prior toxoplasmic encephalitis<br>**Note:** Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens<br>Criteria for Discontinuing Secondary Prophylaxis<br>*If All of the Following Criteria are Fulfilled:*<br>• Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, **and** |

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Secondary Prophylaxis** (Suppressive Therapy), continued | | Children Aged 4–24 Months:<br>• Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/$m^2$ body surface area (maximum 25 mg) by mouth once daily, **plus**<br>• Leucovorin, 5 mg by mouth every 3 days<br>• TMP-SMX, 150/750 mg/$m^2$ body surface area once daily by mouth | • Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months<br>• Aged ≥6 years; CD4 cell count >200 cells/$mm^3$ for >6 consecutive months<br>Criteria For Restarting Secondary Prophylaxis:<br>• Aged 1 to <6 years with CD4 percentage <15%<br>• Aged ≥6 years with CD4 cell count <200 cells/$mm^3$ |
| **Treatment** | Congenital Toxoplasmosis:<br>• Pyrimethamine loading dose—2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, **plus**<br>• Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, **plus**<br>• Sulfadiazine 50 mg/kg body weight by mouth twice daily<br>*Treatment Duration:*<br>• 12 months<br>Acquired Toxoplasmosis<br>*Acute Induction Therapy (Followed by Chronic Suppressive Therapy):*<br>• Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, **plus**<br>• Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, **plus**<br>• Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy<br>Treatment Duration (Followed by Chronic Suppressive Therapy):<br>• ≥6 weeks (longer duration if clinical or radiologic disease | For Sulfonamide-Intolerant Patients:<br>• Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin | Congenital Toxoplasmosis:<br>• For infants born to mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy.<br>Acquired Toxoplasmosis:<br>• Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing.<br>• TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults, but has not been studied in children.<br>• Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/ leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children.<br>• Azithromycin (for adults, 900–1,200 mg/day, corresponding to 20 mg/kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children.<br>• Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible.<br>• Anticonvulsants should be administered to patients with a history of seizures and |

**Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis** (page 3 of 3)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| **Treatment,** continued | is extensive or response in incomplete at 6 weeks) | | continued through the acute treatment; but should not be used prophylactically. |

* **Note:** Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight.

**Key to Acronyms:** cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole

# Varicella-Zoster Virus (Last updated December 9, 2019; last reviewed December 9, 2019)

| Panel's Recommendations |
|---|
| I. **Should children with HIV without evidence of immunity to varicella receive the varicella vaccine, compared to not receiving the vaccine?** |
| • Vaccination with the varicella vaccine should be considered for children with HIV without evidence of immunity to varicella. Administration is considered safe for children with CD4 T lymphocyte (CD4) cell percentage ≥15%. Two doses of varicella vaccine should be given, starting as early as 12 months of age, with an interval of 3 months. Preferably the child will have been on effective antiretroviral therapy (ART) for ≥3 months prior to immunization. **(strong, low)** |
| II. **Should children with HIV who are without evidence of immunity to varicella and exposed to varicella or herpes zoster (HZ) receive prophylaxis with human varicella-zoster immunoglobulin, compared to not receiving varicella-zoster immunoglobulin?** |
| • Children with HIV who are susceptible to varicella and have had a significant exposure to varicella or HZ, and are severely immune compromised, should receive varicella zoster immune globulin (available as VariZIG) as soon as possible within the first 10 days after exposure. The extent of immune compromise should be considered in making this decision. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). **(strong, low)** |
| III. **Should children with HIV with varicella be treated with acyclovir, compared to not being treated with acyclovir?** |
| • Intravenous (IV) acyclovir therapy is recommended for children with HIV with significant immune compromise who have varicella or for any child with HIV with severe varicella. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes efficacy. For select patients with HIV perceived to be at lower risk of developing severe varicella, many experts use oral acyclovir. This decision is made for patients with relatively normal concentrations of CD4 cells, especially if they are receiving ART. **(strong, moderate)** |
| IV. **Should children with HIV with HZ be treated with acyclovir, compared to not being treated with acyclovir?** |
| • Oral therapy with acyclovir for 7 days to 10 days is recommended for children with HIV with HZ, although longer therapy duration should be considered when lesions are slow to resolve. Initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete therapy. **(strong, moderate)** |
| V. **Is foscarnet the best choice for anti-varicella-zoster virus (VZV) therapy for children with HIV in whom therapy is failing because of acyclovir-resistant VZV?** |
| • When acyclovir resistance is considered, if possible, virus isolation should be attempted for susceptibility testing. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. VZV Infections caused by acyclovir-resistant VZV strains should be treated with parenteral foscarnet. **(strong, very low)** |
| Rating System<br>*Strength of Recommendation:* Strong; Weak<br>*Quality of Evidence:* High; Moderate; Low; or Very Low |

## Epidemiology

Varicella-zoster virus (VZV) infections are endemic worldwide. Prior to the universal administration of varicella vaccine, approximately 4 million cases of varicella occurred annually in the United States. The annual incidence in children aged <10 years was 9%; by adulthood >95% of individuals had antibodies to VZV, indicating prior primary varicella infection.[1] In tropical and subtropical areas, varicella may be acquired later in childhood or in early adulthood, but seroprevalence among adults is high by age 30 years. In the United States, the incidence of varicella and its associated morbidity and mortality have decreased by ≥88% because of universal vaccination.[2-4]

VZV is transmitted by an airborne route.[5] Varicella is highly contagious; clinical infection develops in about 80% of susceptible individuals exposed to VZV within a household.[6] Second attacks of varicella are very uncommon.

Perinatal transmission of VZV can occur. However, because most pregnant women have varicella immunity, varicella complicating pregnancy is unusual. Perinatal transmission of VZV has not been reported in pregnant women with HIV who develop varicella. Congenital varicella syndrome (multiple anomalies) occurs in approximately 0.4% of infants born to women who have varicella at 1 week to 12 weeks of pregnancy and in approximately 2% of infants born to women who have varicella at 13 to 20 weeks of pregnancy,[7] but is not seen in infants born to women who develop herpes zoster (HZ) during pregnancy.

VZV also can be transmitted to fetuses in late gestation, resulting in neonatal varicella. In mothers who develop varicella 5 days before to 2 days after delivery, the attack rate for infants is approximately 20%, and mortality, before the availability of antiviral therapy, was approximately 30%.[8] In comparison, if maternal varicella precedes delivery long enough to allow transfer of VZV antibodies across the placenta, infants can still develop varicella in the first 5 days of life, but the infection is rarely severe.

VZV causes both varicella (primary infection; chickenpox) and HZ (reactivation of latent infection; shingles). HZ represents reactivation of VZV that resides in a latent state in neurons in dorsal root and cranial sensory ganglia following varicella. Once established, VZV latency persists for life, but reactivation to cause HZ occurs in approximately 30% of people who had varicella. HZ is less contagious than varicella, but VZV from HZ lesions can spread by direct contact or by an airborne route to cause varicella in susceptible contacts (i.e., never had varicella or never received the varicella vaccine). HZ occurs because VZV-specific cellular immunity, which is first stimulated by primary infection (varicella) and is needed to maintain latency, declines with age. In addition, VZV-specific cellular immunity is also typically depressed by HIV infection, which explains why HZ is common in people with HIV.[9-11] HZ was a very common complication in children with HIV before the advent of antiretroviral therapy (ART) (approximately 10 cases/100 patient-years prior to 1996); the incidence of HZ remains at 2 to 3 cases/100 patient-years in the ART era, which is 10 to 25 times higher than in the general population.[12-15] Risk factors for development of HZ include low incident (i.e., coincidental with HZ reactivation) or nadir CD4 T lymphocyte (CD4) cell count/percentage; high HIV viral load; and acquisition of varicella when the CD4 percentage is <15%.[14,16,17] As in adults, the frequency of HZ recurrences in children correlates inversely with the CD4 count.[14,18] The incidence of HZ increases with age; this trend extends into adulthood, particularly in individuals aged >50 years.

In addition to ART and immune reconstitution, one reason for the declining incidence of HZ in children with HIV in countries with varicella vaccination programs is that many received the licensed varicella vaccine. Varicella vaccination is associated with a decrease in HZ in children without HIV[19,20] compared with those who had wild-type infection. This is also true for vaccinated children with HIV compared with those who had wild-type infection.[21]

## Clinical Manifestations

The incubation period for varicella ranges from 10 to 21 days (average: 14 days) in immunocompetent children. Varicella can be associated with a brief prodrome of malaise and fever, followed by the appearance of skin lesions that are more numerous on the face and trunk than on the extremities. The lesions appear in three or more successive crops over approximately 5 to 7 days. They evolve quickly (in about 24 hours) through macular, papular, vesicular, and pustular stages, culminating in crusts. Combinations of these types of lesions are present simultaneously. Varicella causes more morbidity in patients with HIV than in the general population. Initial reports of varicella in children with HIV suggested severe disease manifestations and chronic, atypical skin lesions.[22,23] Clinically important systemic involvement, especially in severely immune compromised children, can include neurologic manifestations such as encephalitis, cerebellar ataxia, and transverse myelitis; hepatitis; pneumonia; and multiorgan failure with intravascular coagulation. Subsequent studies suggest less complicated varicella infections in children with HIV, particularly in those receiving ART or who have higher CD4 counts at the time of infection.[16,24] However, the disease may last longer than normal, and the rate of complications is higher in children with HIV than in otherwise healthy children with varicella.[25]

Uncommonly, severely immunocompromised children with HIV can have persistent chronic varicella infection, with continued appearance of new VZV lesions for >1 month after onset of varicella.[23,26] The lesions are characteristically varicelliform at onset but evolve into non-healing ulcers or necrotic, crusted, and hyperkeratotic verrucous lesions. Chronic VZV was reported in 14% of children with HIV with VZV in the pre-ART era, usually in children with low CD4 counts.[18]

The classical presentation of HZ is a painful or pruritic, vesicular, dermatomal rash. Typically, pain precedes the rash by 2 to 3 days. Less typical rashes, like those described for chronic varicella, including rashes that extend beyond dermatomal boundaries or are bilaterally distributed or generalized, can occur in children with HIV. These children may also have multiple recurrent episodes of HZ.[14,18] Disseminated HZ with multiorgan involvement can occur, with or without the typical rash of HZ. Encephalitis long after HZ, or without rash, has been reported in children with HIV.[27] Ruling out herpes simplex virus infection, which can be confused with VZV skin manifestations, is important in evaluating children with HIV with possible HZ infection. This can be accomplished by PCR testing of vesicular fluid.

Retinitis is a complication of VZV infection in children and adolescents with HIV[28,29] that can be confused with cytomegalovirus retinitis.[30] Progressive outer retinal necrosis is a VZV-associated entity that typically occurs in patients with CD4 counts <50 cells/mm$^3$ and is often associated with HZ. Acute retinal necrosis can occur in children with HIV at any CD4 count. A rapid decrease in visual acuity, or occurrence of red eye or eye pain, should prompt an immediate consultation with an ophthalmologist for diagnosis and specific therapy.

## Diagnosis

Typical presentations of varicella and HZ are readily diagnosed clinically. Laboratory diagnostic methods are required for atypical presentations, prolonged course of disease, and non-response to therapy. VZV DNA polymerase chain reaction (PCR) is the most sensitive and specific method for diagnosing a VZV infection.[31] The technique can provide an etiologic diagnosis within 24 to 48 hours, and some research laboratories can differentiate between wild-type and vaccine strain VZV. In addition to lesion specimens (vesicular fluid or scabs), PCR can be applied to blood, cerebrospinal fluid, and pharyngeal and conjunctival swabs. Direct immunofluorescence for VZV antigen can be performed on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Optimal sensitivity requires obtaining cells from the base of a lesion after unroofing a fresh vesicle. This method requires only a 3-hour turnaround time, but is significantly less sensitive (detecting <75% of infections) than PCR.[32,33] VZV can be isolated in cell culture from vesicular fluid or ulcer swabs, but the virus is labile and specimens must be processed rapidly. Typical cytopathic effect is noted only after 5 to 7 days. The more rapid shell vial method, which combines centrifugation of samples onto tissue culture monolayers and staining with fluorescein-conjugated monoclonal antibodies to detect synthesis of early VZV proteins, requires at least 48 hours and is less sensitive than PCR.[32] Culture methods are most often positive when an ulcer or vesicle is sampled, especially during the early days after illness onset and before initiation of antiviral therapy. PCR results are positive if scabs are used as a sample late in the illness. PCR is critical for evaluating atypical presentations of HZ. Serologic tests are of little value in diagnosing active VZV infection in children either with or without HIV.

## Prevention Recommendations

### *Preventing Exposure*

Children with HIV without evidence of immunity to varicella (no verified history of varicella or HZ and no evidence of appropriate vaccination or varicella immunity by a sensitive, specific antibody assay) should avoid exposure to individuals with varicella or HZ. Commercially available VZV antibody assays can have false-negative and false-positive results, limiting the ability to determine varicella immunity with certainty.[31,34] Household contacts who lack evidence of immunity should receive varicella vaccine to reduce the possibility of transmitting wild-type VZV to their contacts who have HIV.[35] For the same reason, elderly household contacts should receive the HZ vaccine according to Advisory Committee on Immunization Practices (ACIP) recommendations.[36]

## *Preventing Disease*

### Active Immunization

Children with HIV aged 1 year to 8 years without evidence of immunity to varicella who have CD4 percentages ≥15% should be considered for two doses of varicella vaccine, the first dose administered as soon as possible after the first birthday and the second dose 3 months later.[35] Limited data from a clinical trial in children with HIV with these two characteristics indicate that the vaccine was well tolerated and that >80% of the children had detectable VZV-specific immune responses (either antibody or cell-mediated immune response or both) at 1 year after vaccination.[37,38] This finding has been validated by other investigators, including persistence of antibody for up to 7 years or more post-vaccination.[39-42] In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered in place of the single-antigen varicella vaccine to children with HIV.

Data are limited on use of varicella vaccine in older children and adolescents with HIV. However, the safety of varicella vaccine in individuals with HIV aged >8 years who have comparable levels of immune function is likely to be similar to that in younger children, although immunogenicity in individuals without HIV is lower as the age of the vaccination increases. Weighing potential risks and benefits favors administering two doses of varicella vaccine, 3 months apart, to older patients without evidence of immunity providing that they have CD4 percentages ≥15% and CD4 counts ≥200 cells/mm$^3$. The response to vaccination is optimal in patients on effective ART for an extended period and in those with high CD4 counts and very low viral loads.[42,43] This should be considered in scheduling varicella (and other) vaccinations to elicit optimal immune responses.

Although children with HIV who are not severely immunocompromised tolerate the vaccine well, they, like healthy children, infrequently develop mild rashes around 2 to 3 weeks after vaccination. Antiviral therapy is rarely required, and skin lesions usually clear in 3 days to 5 days without treatment. Vaccine-strain VZV is susceptible to acyclovir, should antiviral treatment be necessary. Because there is still wild-type varicella circulating, albeit at low levels, VZV rashes (especially when they are extensive) that develop shortly after vaccination require virologic investigation to distinguish vaccine-associated rashes from those caused by wild-type VZV. HZ from the vaccine strain (Oka) occurs in vaccinated healthy children, although at a much lower rate than among those who had natural varicella infection.[20,44] Data on the frequency of HZ from vaccination in children with HIV is lacking.

Children with HIV with low CD4 percentages (<15%) may rarely develop systemic disease (i.e., pneumonia and neurologic manifestations) from vaccine-strain VZV and should not be vaccinated against varicella.[45] However, the varicella vaccine can be safely administered to children in whom stable immune reconstitution (i.e., CD4 percentage ≥15%) is achieved with ART for ≥3 months.[38,40]

Effectiveness of the varicella vaccine in children with HIV is suggested by long-term follow-up studies of vaccinees at several institutions.[13,21] Vaccination (one or two doses) was 82% effective against varicella, and no cases of HZ were observed in vaccinees. This compares favorably with the efficacy of the vaccine in healthy children (after one dose) and in children with underlying leukemia (after two doses), where an efficacy of 80% to 85% was observed for prevention of clinical infection. In vaccinated children without HIV, most breakthrough varicella cases (i.e., varicella that occurs ≥42 days after receipt of varicella vaccine) are mild, with fewer lesions (commonly <50) and less fever and a shorter duration of illness than with varicella in unvaccinated children.[46,47] Comprehensive information on the severity of breakthrough varicella in children with HIV is lacking.

Because HZ vaccine is licensed only for use in healthy people aged ≥50 years to prevent HZ and has not been studied in children with HIV, it should not be given to children with HIV.

### Passive Immunization

Published guidelines indicate that children and adolescents with HIV who lack evidence of immunity to varicella (as defined by ACIP),[35] and have a non-transient, significant exposure to a person with varicella or HZ should receive human VZV immunoglobulin (VariZIG) prophylaxis as soon as possible after close contact with the person, ideally within 96 hours but potentially beneficial up to 10 days.[48] However, most experts limit this recommendation to varicella- or zoster-exposed children with HIV who are considered to be severely immunocompromised (i.e., CDC Immunologic Category 3 or Clinical Category C with a high HIV RNA plasma viral load and/or a Clinical Stage 3-defining opportunistic infection)[48] because varicella complications are not increased in such children. Some experts prefer to see these children on ART for ≥3 months and have a CD4 count ≥200/mm$^3$.

Passive immunization is achieved with VariZIG, a liquid which, when properly reconstituted, is a 5% solution of hyperimmune Immunoglobulin G that can be administered intramuscularly. VariZIG is commercially available in the United States from a broad network of specialty distributors (list available on the VariZIG website). The incubation period for varicella may be prolonged up to 28 days after VariZIG administration, thus also extending the period of potential infectiousness. VariZIG may attenuate, but not prevent varicella, in which case the patient will be potentially infectious.[49] Subsequent active immunization, provided the vaccine is not contraindicated (and if varicella does not develop), should be delayed for 5 months. If VariZIG is not available, intravenous immune globulin (IVIG), 400 mg/kg body weight, administered once as soon as possible (ideally within 96 hours after exposure), can be used. However, the titer of anti-VZV antibodies of any specific lot of IVIG is uncertain because IVIG is not tested routinely for anti-VZV antibodies. Patients who have received the specified dose of IVIG within 3 weeks prior to varicella- or zoster-exposure should be protected. When passive immunization is not possible for severely immunocompromised patients, some experts recommend oral acyclovir for post-exposure prophylaxis (see below).

#### Post-Exposure Antiviral Prophylaxis

Several small studies suggest that post-exposure prophylaxis with oral acyclovir often prevents or attenuates varicella in healthy children,[50-52] although this approach is predicated on adequate specific immune responses developing in the exposed child during the incubation period. When passive immunization is not possible, some experts recommend prophylaxis with oral acyclovir 20 mg/kg body weight (maximum dose 800 mg), administered 4 times daily for 7 days, beginning 7 days to 10 days after exposure.[53] The use of acyclovir for prophylaxis in VZV-exposed children with HIV has not been studied. For that reason, while some experts would recommend post-exposure prophylaxis with acyclovir beginning 7 days to 10 days after exposure, other experts consider it prudent to wait until rash appears to start acyclovir therapy in VZV-susceptible, VZV-exposed, children with HIV who were not given passive immunization.

#### Post-Exposure Prophylaxis with Varicella Vaccine

Post-exposure prophylaxis with varicella vaccine has been successfully used in children and adults without HIV.[54] However, this preventive approach is predicated on a prompt and robust immune response, which is why it has not been studied in patients with HIV and is not recommended.

## Treatment Recommendations

### *Treating Disease*

Based on controlled trials in children with malignancies,[55,56] and response to therapy in children with HIV severely ill with varicella,[22] acyclovir is the drug of choice for treating varicella infections. Acyclovir should be initiated as soon as possible after varicella lesions appear. In immune competent children, new lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all lesions may take 5 days to 7 days. In children with HIV, intravenous (IV) acyclovir is recommended to treat varicella in those with severe immunosuppression (CDC Immunologic Stage 3) and those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions. For children aged <1 year, the dose of acyclovir is 10 mg/kg body weight administered IV every 8 hours as a 1-hour infusion. Some health care providers administer the same dose to older children, while others base the dose of acyclovir in older children on body surface area (500 mg/m$^2$ IV every 8 hours as a 1-hour infusion).[53] Administration is for 7 days to 10 days, provided at least 48 hours have elapsed since the appearance of new lesions. The decision may be made to complete therapy with oral acyclovir. In children with HIV, initial treatment of varicella with oral acyclovir should only be considered for patients considered mildly to moderately immune suppressed and who have mild varicella disease.

Acyclovir 20 mg/kg body weight (800 mg maximum dose) administered 4 times per day for 7 days to 10 days is the oral treatment of choice for HZ in children with HIV, although a longer duration of therapy should be considered when lesions are slow to resolve. Oral administration of acyclovir for HZ is considered safe because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. However, initial IV administration of acyclovir is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ and may also be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete the course of therapy (10 days to 14 days in this situation). Doses of IV acyclovir for treating HZ are the same as those for treating varicella.

Progressive outer retinal necrosis evolves rapidly, and despite aggressive therapy, the prognosis for visual preservation is poor. Involvement of an ophthalmologist with experience in managing VZV ocular disease and its complications in children is strongly recommended when ocular involvement is evident. Optimal therapy for the retinopathy has not been defined. Regardless of specific VZV antiviral therapy, optimization of ART is recommended and monitoring for the emergence of immune reconstitution inflammatory syndrome (IRIS) is warranted, particularly among ART-naive children (see below). Most experts recommend IV anti-VZV therapy that includes combinations of systemic antivirals (acyclovir or ganciclovir plus foscarnet), frequently given in conjunction with twice-weekly intravitreal injections of ganciclovir and/or foscarnet.[57-59] Adjunctive retinal surgery is sometimes recommended, along with corticosteroids and/or low-dose aspirin for associated occlusive vasculopathy and optic neuropathy. In contrast to progressive outer retinal necrosis, acute retinal necrosis appears more responsive to high-dose IV acyclovir (10–15 mg/kg body weight IV every 8 hours for 10 days to 14 days), followed by prolonged (i.e., 4 weeks to 6 weeks) oral treatment with acyclovir, or valacyclovir for older patients.[60,61]

Alternatives to oral acyclovir for varicella and HZ in older adolescents and adults include valacyclovir and famciclovir. Valacyclovir is a prodrug of acyclovir with improved bioavailability, which is rapidly converted to acyclovir after absorption. Sufficient information exists to support the use of valacyclovir in children (especially given its improved bioavailability, which is two- to three-fold that of acyclovir) at a dose of valacyclovir 20 to 25 mg/kg body weight administered two to three times a day. Doses lower than this may be insufficient for children weighing <20 kg.[62-64] No pediatric formulation is available, and valacyclovir can generally only be used for children old enough to swallow the large tablets, although crushed valacyclovir tablets can be used to make an extemporaneous suspension with good bioavailability.[63,65] A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation or are too small for available pills. A schedule for weight-adjusted dosing is available to inform dosing of small children.[66]

### *Monitoring and Adverse Events, Including IRIS*

Primary toxicities of acyclovir are phlebitis (when acyclovir is administered IV), renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir and famciclovir. In infants receiving high-dose acyclovir for neonatal HSV disease, the major side effect was neutropenia (defined as absolute neutrophil count $<1,000/mm^3$).[67] Among severely ill children without HIV receiving high-dose IV acyclovir, renal injury or failure was observed in >10% of patients.[68] Renal function should be assessed upon initiation of acyclovir treatment and at least once weekly during treatment, especially in patients with underlying renal dysfunction who are receiving prolonged therapy. If possible, avoid concomitant administration of other nephrotoxic drugs. IV acyclovir must be adequately diluted and administered slowly over 1 to 2 hours. Since acyclovir is excreted primarily by the kidneys, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure.

HZ has been considered an IRIS event in numerous reports in which the incidence of HZ was increased transiently after institution of ART.[69] However, an analysis that compared the incidence of HZ in children in the 3 months before ART initiation to that in the 3 months after ART initiation indicated no difference in incidence rates.[14] This suggests that the high incidence occurring in the 3 months after ART is initiated represents persistence of the inability to develop a robust VZV-specific cell-mediated immune response in this early post-ART initiation period. As immune reconstitution proceeds beyond this time, the incidence of HZ declines. This relationship has been demonstrated with numerous opportunistic infections[70] and confirmed for HZ.[13]

### *Managing Treatment Failure*

Children in whom lesions continue to develop, fail to heal, or progress after 7 days of treatment may have acyclovir-resistant VZV.[71] This reflects the fact that acyclovir is a virostatic drug and that, in such cases, the patient has inadequate VZV-specific cell-mediated immunity to rapidly clear the VZV infection. If possible, virus isolation should be attempted so that susceptibility testing can be performed to confirm drug resistance. As this may be difficult to arrange and will involve significant delay, the decision to change therapy is often based on clinical observations. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. The therapeutic choice for acyclovir-resistant VZV is foscarnet, 40 to 60 mg/kg body weight per dose, which should be administered IV 3 times daily for 7 days or until no new lesions have appeared for at least 48 hours.[60,72] Foscarnet should be administered slowly IV over the course of 2 hours (no faster than 1 mg/kg/minute).

Foscarnet has significant nephrotoxic potential; ≥30% of patients experience increases in serum creatinine. Foscarnet also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and central nervous system symptoms can occur. Infusing foscarnet with saline fluid loading can minimize renal toxicity, and infusion through a central venous catheter can prevent thrombophlebitis. Doses should be modified in patients with renal insufficiency (see package insert). For patients receiving foscarnet, CBCs, serum electrolytes, and renal function should be monitored at least 2 to 3 times per week during induction therapy and once weekly thereafter.

### *Preventing Recurrence*

No measures are available to prevent HZ in children and adolescents with HIV. However, varicella vaccination reduces the incidence (and perhaps severity) of HZ such that the risk of HZ is lower in vaccinated children with HIV than in healthy children or children with HIV who had naturally acquired varicella.[13,21,73] The likelihood of initial or recurrent attacks of HZ is reduced with effective ART.[14] A live attenuated vaccine (Zoster Vaccine Live, ZVL) and an inactive recombinant vaccine (Recombinant Zoster Vaccine, RZV) have been approved for use in adults aged ≥50 years.[36,74] A large study of the recombinant vaccine in adults with HIV indicated that it was safe and induced VZV-specific antibody and cell-mediated immunity in vaccines on ART with CD4 percentage ≥15.[75] Although there are no efficacy data for this vaccine in adults with HIV, it is frequently administered to adults with HIV who meet these criteria. This vaccine has not been studied in children.[76]

### *Discontinuing Secondary Prophylaxis*

Not applicable.

## Recommendations

### *Prevention*

**I. Should children with HIV without evidence of immunity to varicella receive the varicella vaccine, compared to not receiving the varicella vaccine?**

- Children with HIV without evidence of immunity to varicella should be considered for the varicella vaccine. Vaccine administration is considered safe for children with CD4 percentage ≥15%. Two doses of varicella vaccine should be given, starting as early as 12 months of age, with an interval of 3 months. Preferably the child will have been on effective ART for ≥3 months prior to vaccination. **(strong, low)**

- Vaccine administration is considered safe for children with HIV with CD4 percentage ≥15%. Limited data from clinical trials in such children indicate that the vaccine was well-tolerated and that >80% of the children had detectable VZV-specific immune responses (either antibody or cell-mediated immune response or both) at 1 year after vaccination.[37,38] Two doses of varicella vaccine should be given, starting as soon as possible after 12 months of age, with an interval of 3 months. Preferably the child will have been on ART for ≥3 months prior to immunization. In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered in place of the single-antigen varicella vaccine to children with HIV. Effectiveness of the varicella vaccine in children with HIV is suggested by long-term follow-up studies.[13,21] Vaccination was 82% effective against varicella, and no cases of HZ were observed in vaccinees. Comparable efficacy was reported in vaccinated healthy children (after one dose) and in vaccinated children with underlying leukemia (after two doses), where an efficacy of 80% to 85% was observed for prevention of clinical infection.

**II. Should children with HIV who are without evidence of immunity to varicella and exposed to varicella or HZ receive prophylaxis with human varicella-zoster immunoglobulin, compared to not receiving varicella-zoster immunoglobulin?**

- Children with HIV who are susceptible to varicella and have had a significant exposure to varicella or HZ, and are severely immune compromised, should receive varicella zoster immune globulin (available as VariZig) as soon as possible within 10 days after exposure. The extent of immune compromise should be considered in making this decision. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). **(strong, low)**
- Children with HIV who are susceptible to varicella and are severely immunocompromised, and have had an exposure to varicella or HZ, are likely to develop severe varicella with complications. A large observational study of immunocompromised children, without HIV infection, indicated that varicella zoster immune globulin (currently available as VariZig) given within 72 hours of exposure reduced varicella severity compared to historical controls.[49] Subsequent studies indicated that some protection occurred with passive immunization as long as 10 days after exposure.[77] Thus, varicella- or HZ-exposed children with HIV are likely to benefit from passive immunization **(strong, low)**, although most experts limit this recommendation to those who are considered to be severely immunocompromised. VariZig is given intramuscularly at the recommended dose of 125 units/10 kg, up to a maximum of 625 units (i.e., 5 vials). If VariZig is unavailable, immune globulin for IV administration can be used at the dose of 400 mg/kg. VariZIG may attenuate, but not prevent varicella, in which case the patient will be potentially infectious. If passive immunization is not possible for severely immunocompromised patients, some experts recommend oral acyclovir for post-exposure prophylaxis.

## *Treatment*

**III. Should children with HIV with varicella be treated with acyclovir, compared to not being treated with acyclovir?**

- IV acyclovir therapy is recommended for children with HIV with significant immune compromise who have varicella or for any child with HIV with severe varicella. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes efficacy. For select patients with HIV perceived to be at lower risk of developing severe varicella, many experts use oral acyclovir. This decision is made for patients with relatively normal concentrations of CD4 cells, especially if they are receiving ART. **(strong, moderate)**

- On the basis of controlled trials treating severe varicella in children with malignancy[55,56] and of observational studies treating the disease in children with HIV,[22] IV acyclovir is recommended as initial therapy in children with HIV with severe immunosuppression. Treatment should be initiated as soon as possible (especially within 24 hours) after varicella lesions appear to maximize efficacy. Many experts use oral acyclovir for select children with HIV perceived to be at lower risk of developing severe varicella. However, the decision to use oral acyclovir is reserved for patients with relatively normal concentrations of CD4 cells, especially if they are receiving ART. IV administration should also be considered for children with high fever; abdominal pain; respiratory symptoms; numerous or deep, necrotic, or hemorrhagic skin lesions; disseminated infection; or visceral involvement. Administration is for 7 days to 10 days, provided that new lesions have ceased to appear for at least 48 hours. The decision may be made to complete 10 days to 14 days of therapy with oral acyclovir.

**IV. Should children with HIV with HZ be treated with acyclovir, compared to not being treated with acyclovir?**

- Oral therapy with acyclovir for 7 days to 10 days is recommended for children with HIV with HZ, although longer therapy duration should be considered if lesions are slow to resolve. Initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete therapy. **(strong, moderate)**
- Oral acyclovir therapy for HZ for 7 days is established therapy in immune competent patients,[78] and IV therapy was demonstrably efficacious in a controlled trial in immunocompromised patients, including those with disseminated HZ.[79] Oral acyclovir for 7 days to 10 days is recommended for HZ in children with HIV, although longer therapy duration should be considered if lesions are slow to resolve. However, initial IV administration is recommended for children with HIV with severe immunosuppression, extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete 10 to 14 days of therapy.

**V. Is foscarnet the best choice for anti-varicella-zoster virus (VZV) therapy for children with HIV in whom therapy is failing because of acyclovir-resistant VZV?**

- When acyclovir resistance is considered, if possible, virus isolation should be attempted for susceptibility testing. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. VZV infections caused by acyclovir-resistant VZV strains should be treated with parenteral foscarnet. **(strong, very low)**
- Children in whom lesions continue to develop, fail to heal, or continue to progress after 7 days of treatment may have acyclovir-resistant VZV.[71] Isolation of persisting virus should be attempted so that susceptibility testing can be performed to confirm drug resistance. Since this involves considerable delay, the decision to change therapy is often based on clinical observations. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. Based on this finding and three observational or open-label studies, primarily in adults, that documented responses to foscarnet, this second line drug is the therapeutic choice for acyclovir-resistant VZV.[72,80,81] Foscarnet (40–60 mg/kg/dose IV every 8 hours) is administered for 7 days to 10 days or until no new lesions appear.

## Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus (page 1 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Pre-Exposure Prophylaxis | Varicella vaccine | N/A | See Figure 1 for detailed vaccine recommendations. |
| Primary (Post-Exposure) Prophylaxis | VariZIG 125 IU/10 kg body weight (maximum 625 IU) IM, administered ideally within 96 hours (potentially beneficial up to 10 days) after exposure | If VariZIG is not available, IVIG 400 mg/kg body weight, administered once should be considered. IVIG should ideally be administered within 96 hours of exposure.<br><br>When passive immunization is not possible, some experts recommend prophylaxis with acyclovir 20 mg/kg body weight/dose (maximum dose acyclovir 800 mg) by mouth, administered four times a day for 7 days, beginning 7–10 days after exposure. | Primary Post-Exposure Prophylaxis Indicated for:<br>• Patients with substantial exposure to varicella or zoster who have no verified history of varicella or zoster, *or* who are seronegative for VZV on a sensitive, specific antibody assay, or who lack evidence of vaccination.<br>• Many experts limit the recommendation for passive immunization to varicella- or zoster-exposed children with HIV considered severely immunocompromised (i.e., CDC Immunologic Category 3), especially if severely symptomatic (i.e., CDC Clinical Category C[a]) and experiencing a high HIV RNA plasma viral load.<br>• Some experts start acyclovir at first appearance of rash in children with HIV, rather than providing acyclovir as prophylaxis.<br><br>Note: VariZIG is commercially available in the United States from a broad network of specialty distributors.<br><br>[a] Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children aged <13 years. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR Morb Mortal Wkly Rep*. 1994;43:1-19. Available at: http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf. |
| Secondary Prophylaxis | N/A | N/A | There is no indication for secondary prophylaxis. |
| Treatment | Varicella<br><br>*Children with No or Moderate Immune Suppression (CDC Immunologic Categories 1 and 2) and Mild Varicella Disease:*<br>• Acyclovir 20 mg/kg body weight/dose by mouth (maximum 800 mg/dose) four times a day for 7–10 days and until no new lesions for 48 hours<br><br>*Children with Severe Immune Suppression or Severe Varicella Disease (see text):*<br>• Acyclovir 10 mg/kg body weight or 500 mg/m²/dose IV every 8 hours for 7–10 days and until no new lesions for 48 hours | Patients Unresponsive to Acyclovir:<br>• Foscarnet (40–60 mg/kg body weight/dose IV every 8 hours) for 7-10 days or until no new lesions have appeared for 48 hours | In children aged ≥1 year, some experts base IV acyclovir dosing on body surface area (500 mg/m² body surface area/dose IV every 8 hours) instead of body weight.<br><br>Valacyclovir is approved for use in adults and adolescents with zoster at 1 g/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. Valacyclovir can be used in children at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day. Doses lower than this may be insufficient for children weighing <20 kg. There is no pediatric preparation, although 500-mg capsules can be extemporaneously compounded to make a suspension to administer valacyclovir 20 mg/kg body weight/dose (maximum dose 1 g) given three times a day (see prescribing information).<br><br>Famciclovir is approved for use in adults and adolescents with zoster at 500 mg/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation. A schedule for weight-adjusted dosing is available to inform dosing of small children. |

**Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus** (page 2 of 2)

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Treatment, continued | Zoster<br>*Children with Uncomplicated Zoster and No or Moderate Immune Suppression:*<br>• Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth four times a day for 7–10 days<br>*Children with Severe Immunosuppression (CDC Immunologic Category 3), Trigeminal or Sacral Nerve Involvement, Extensive Multidermatomal, or Disseminated Zoster:*<br>• Acyclovir 10 mg/kg body weight/dose or 500 mg/m$^2$ IV every 8 hours until cutaneous lesions and visceral disease are clearly resolving, then patient can switch to oral acyclovir to complete a 10–14-day course<br>*Children with Progressive Outer Retinal Necrosis:*<br>• Acyclovir (10 mg/kg or 500 mg/m$^2$ every 8 hours) or ganciclovir 5 mg/kg body weight/dose IV every 12 hours, plus<br>• Foscarnet 90 mg/kg body weight/dose IV every 12 hours, plus<br>• Ganciclovir 2 mg/0.05 mL intravitreal injection twice weekly and/or foscarnet 1.2 mg/0.05 mL intravitreal injection twice weekly<br>*Children with Acute Retinal Necrosis:*<br>• Acyclovir 10–15 mg/kg body weight/dose IV every 8 hours daily for 10–14 days, followed by oral valacyclovir 1 g/dose three times a day for 4–6 weeks (for children old enough to receive adult dose).<br>• Alternative to oral valacyclovir is oral acyclovir 20 mg/kg body weight/dose four times a day for 4–6 weeks | | Involvement of an ophthalmologist with experience in managing HZ ophthalmicus and its complications in children is strongly recommended when ocular involvement is evident.<br>Optimal management of progressive outer retinal necrosis has not been defined. |

Key: CDC = Centers for Disease Control and Prevention; HZ = herpes zoster; IM = intramuscular; IU = international units; IV = intravenous; IVIG = intravenous immunoglobulin; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus

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# Appendix A. Key to Acronyms

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## Drug and Vaccine Name Abbreviations

| Abbreviation | Full Name |
|---|---|
| 3TC | Lamivudine |
| 5-FU | 5-fluorouracil |
| 9vHPV | 9-valent human papillomavirus [vaccine] |
| ABLC | amphotericin B lipid complex |
| BCA | bichloroacetic acid |
| BCG | Bacille Calmette-Guérin [vaccine] |
| DEET | N,N-diethyl-meta-toluamide |
| DTaP | diphtheria, tetanus, and acellular pertussis [vaccine] |
| EFV | efavirenz |
| FTC | emtricitabine |
| HBIG | hepatitis B immune globulin |
| HepA | hepatitis A [vaccine] |
| HepB | hepatitis B [vaccine] |
| IIV | inactivated influenza vaccine |
| IPV | inactivated polio vaccine |
| IVIG | intravenous immune globulin |
| LAIV | live attenuated influenza vaccine |
| L-AmB | liposomal amphotericin B |
| MCV | meningococcal conjugate vaccine |
| MenACWY | meningococcal strains A, C, W, Y [vaccine] |
| MMR | measles, mumps, and rubella [vaccine] |
| MMRV | measles, mumps, rubella, and varicella [vaccine] |
| NVP | nevirapine |
| PCV | pneumococcal conjugate vaccine |
| PCV13 | 13-valent pneumococcal conjugate vaccine |
| PCV7 | 7-valent pneumococcal conjugate vaccine |
| Peg-IFN-α | pegylated interferon-alpha |
| PPSV | pneumococcal polysaccharide vaccine |

| | |
|---|---|
| PPSV23 | pneumococcal polysaccharide vaccine (23-valent) |
| RV | rotavirus vaccine |
| RZV | recombinant zoster vaccine |
| TCA | trichloroacetic acid |
| Td | tetanus and diphtheria [vaccine] |
| Tdap | tetanus and diphtheria toxoids and acellular pertussis [vaccine] |
| TMP-SMX | trimethoprim-sulfamethoxazole |
| TPOXX | tecovirimat |
| YFV | yellow fever vaccine |
| ZVL | zoster vaccine live |

## General Terms

| Acronym | Definition |
|---|---|
| A-a | alveolar-arterial |
| AAFP | American Academy of Family Physicians |
| AAP | American Academy of Pediatrics |
| ACIP | Advisory Committee on Immunization Practices |
| ACOG | American College of Obstetricians and Gynecologists |
| AFB | acid-fast bacteria |
| AFP | alpha-fetoprotein |
| AIN | anal intraepithelial neoplasia |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ARDS | acute respiratory distress syndrome |
| ARN | acute retinal necrosis |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| ASCCP | American Society for Colposcopy and Cervical Pathology |
| ASC-H | atypical squamous cells—cannot exclude a high-grade intraepithelial lesion |
| ASC-US | atypical squamous cells of undetermined significance |
| BID | twice daily |
| BP | blood pressure |
| BSA | body surface area |
| BUN | blood urea nitrogen |

| Acronym | Definition |
|---|---|
| cART | combination antiretroviral therapy |
| CBC | complete blood count |
| CD4 | CD4 T lymphocyte |
| CDC | Centers for Disease Control and Prevention |
| CF | complement fixation |
| CFU | colony-forming unit |
| CI | confidence interval |
| CIN | cervical intraepithelial neoplasia |
| CIN1 | cervical intraepithelial neoplasia-1 |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| Cr | creatinine |
| CrCl | creatinine clearance |
| CSF | cerebrospinal fluid |
| CT | computerized tomography |
| CYP450 | cytochrome P450 |
| DFA | direct fluorescent antibody |
| DOT | directly observed therapy |
| DST | drug susceptibility test |
| EIA | enzyme immunoassay |
| EKG | electrocardiogram |
| ESRD | end stage renal disease |
| EVR | early virologic response |
| FDA | U.S. Food and Drug Administration |
| FTA-ABS | fluorescent treponemal antibody absorption |
| G6PD | glucose-6-phosphate dehydrogenase |
| GI | gastrointestinal |
| H | hemagglutinin |
| HAB | hepatitis B (rDNA) |
| HAI | hemagglutination inhibition |
| HAV | hepatitis A virus |
| HBc | hepatitis B core antigen |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |

| Acronym | Definition |
|---|---|
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HEU | HIV-exposed but uninfected |
| HHS | U.S. Department of Health and Human Services |
| HHV-8 | human herpesvirus-8 |
| Hib | Haemophilus influenzae type b |
| HIV-1 | human immunodeficiency virus 1 |
| HIVMA | HIV Medicine Association |
| HPV | human papillomavirus |
| HRA | high-resolution anoscopy |
| HSIL | high-grade squamous intraepithelial lesion |
| HSV | herpes simplex virus |
| HSV-1 | herpes simplex virus type 1 |
| HSV-2 | herpes simplex virus type 2 |
| HZ | herpes zoster |
| ICP | intracranial pressure |
| IDSA | Infectious Diseases Society of America |
| IFN | interferon |
| IFN-α | interferon-alfa |
| IFN-γ | interferon-gamma |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IGRA | interferon-gamma release assay |
| IL28B | interleukin-28 |
| IM | intramuscular |
| IND | investigational new drug |
| IPD | invasive pneumococcal disease |
| IRIS | immune reconstitution inflammatory syndrome |
| IU | international unit |
| IV | intravenous |
| JCV | JC (John Cunningham) virus |
| JORRP | juvenile-onset recurrent respiratory papillomatosis |
| KS | Kaposi sarcoma |

| Acronym | Definition |
|---|---|
| KSHV | Kaposi sarcoma–associated herpesvirus |
| KS-IRIS | Kaposi sarcoma–associated immune reconstitution inflammatory syndrome |
| LAM | lipoarabinomannan |
| LEEP | loop electrosurgical excision procedure |
| LFT | liver function test |
| LIP | lymphocytic interstitial pneumonitis |
| LSIL | low-grade squamous intraepithelial lesion |
| LTBI | latent tuberculosis infection |
| LV-PVA | low-viscosity polyvinyl alcohol |
| MAC | Mycobacterium avium complex |
| MDR | multidrug-resistant |
| MDR-TB | multidrug-resistant tuberculosis |
| MRI | magnetic resonance imaging |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| MSM | men who have sex with men |
| MTCT | mother-to-child transmission |
| mtLSU | mitochondrial large subunit |
| N | neuraminidase |
| NAAT | nucleic acid amplification test |
| NCCN | National Comprehensive Cancer Network |
| NCCR | non-coding control region |
| NIH | National Institutes of Health |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSAID | nonsteroidal anti-inflammatory drug |
| NTM | nontuberculous mycobacteria |
| OAR | Office of AIDS Research |
| OARAC | Office of AIDS Research Advisory Council |
| OI | opportunistic infection |
| OPC | oropharyngeal candidiasis |
| OR | odds ratio |
| $PaO_2$ | partial pressure of oxygen |
| PART | presumptive anti-relapse therapy |
| PCP | *Pneumocystis jirovecii* pneumonia |

| Acronym | Definition |
|---|---|
| PCR | polymerase chain reaction |
| PDH | progressive disseminated histoplasmosis |
| PI | protease inhibitor |
| PICO | Population of interest, Intervention being considered, Comparison intervention or condition, and Outcomes of interest |
| PIDS | Pediatric Infectious Disease Society |
| PI-IBS | post-infection irritable bowel syndrome |
| PK | pharmacokinetic |
| PML | progressive multifocal leukoencephalopathy |
| PMTCT | prevention of mother-to-child transmission |
| QFT | QuantiFERON-TB |
| QID | four times daily |
| QTc | QT corrected for heart rate |
| RDT | rapid diagnostic test |
| RIDT | rapid influenza diagnostic test |
| RPR | rapid plasma reagin |
| RR | relative risk; risk ratio |
| RT | reverse transcription |
| RT-PCR | reverse transcription–polymerase chain reaction |
| RVR | rapid virological response |
| SAF | sodium acetate-acetic acid-formalin |
| SC | squamous cell |
| SIL | squamous intraepithelial lesion |
| SJS | Stevens-Johnson Syndrome |
| SMR | sexual maturity rating |
| SQ | subcutaneous |
| STD | sexually transmitted disease |
| SVR | sustained virologic response |
| TB | tuberculosis |
| TBM | tuberculous meningitis |
| TDM | therapeutic drug monitoring |
| TE | *Toxoplasma* encephalitis |
| TID | three times daily |
| TP-PA | *T. pallidum* particle agglutination |

| Acronym | Definition |
|---|---|
| TST | tuberculin skin test |
| ULN | upper limit of normal |
| USPHS | U.S. Public Health Service |
| VAERS | Vaccine Adverse Event Reporting System |
| VaIN | vaginal intraepithelial neoplasia |
| Var | varicella |
| VDRL | Venereal Disease Research Laboratory |
| VIN | vulvar intraepithelial neoplasia |
| VZV | varicella-zoster virus |
| WBC | white blood cell |
| WHO | World Health Organization |
| XDR | extensively drug-resistant |
| XDR-TB | extensively drug-resistant tuberculosis |
| YMDD | tyrosine-methionine-aspartate-aspartate |

## Study and Trial Names

| Acronym | Name |
|---|---|
| PACTG | Pediatric AIDS Clinical Trials Group |

# Appendix B. Important Guideline Considerations

Updated: August 5, 2022
Reviewed: August 5, 2022

**NIH-CDC-HIVMA/IDSA-PIDS-AAP Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV**

| Topic | Comment |
|---|---|
| Goal of the Guidelines | Provide guidance to HIV care practitioners on the prevention and management of HIV-related opportunistic infections for children with and exposed to HIV in the United States. |
| Panel Members | The Panel on the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV (the Panel) is composed of the Executive Secretary and two non-governmental co-chairs with expertise in pediatric HIV infection and infectious diseases. The Panel has members who represent the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the HIV Medical Association of the Infectious Disease Society of America (HIVMA/IDSA), the Pediatric Infectious Disease Society (PIDS), the American Academy of Pediatrics (AAP), plus approximately 55 members with expertise in HIV clinical care, infectious disease management, and research in children. The Panel members are selected from government, academia, and the health care community by the Executive Secretary and co-chairs and assigned to a working group for one or more of the guidelines' sections based on the member's area of subject-matter expertise. Each working group is chaired by a Panel member selected by the co-chairs. Members serve on the Panel for a 4-year term, with an option to be reappointed for additional terms. The list of the current working group members can be found in Appendix C. |
| Financial Disclosure and Management of Conflicts of Interest | All members of the Panel submit an annual written financial disclosure reporting any associations with manufacturers of drugs, vaccines, medical devices, or diagnostics used to manage HIV-related opportunistic infections. A list of these disclosures and the date of their last update are available in Appendix D. The Panel co-editors review each reported association for potential conflict of interest and determine the appropriate action: disqualification from the Panel, disqualification/recusal from topic review and discussion, or no disqualification needed. A conflict of interest is defined as any direct financial interest related to a product addressed in the section of the guidelines to which a Panel member contributes content. Financial interests include direct receipt by the Panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. Financial interest also includes direct compensation for membership on an advisory board, data safety monitoring board, or speakers' bureau. Compensation and support that is awarded to a working group member's university or institution (e.g., grants, research funding) are not considered a conflict of interest. |
| Users of the Guidelines | Pediatric HIV treatment providers in the United States |
| Developer | Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV—a working group of the NIH Office of AIDS Research (OAR) Advisory Council |
| Funding Source | OAR, NIH |

| Topic | Comment |
|---|---|
| Other Guidelines | These guidelines focus on prevention and treatment of HIV-related opportunistic infections for children with or exposed to HIV, including prepubertal adolescents, in the United States. A separate set of guidelines outlines similar recommendations for post-pubertal adolescents and adults. These guidelines are also available on the Clinicalinfo website. |
| Update Plan | Each working group lead (chair) and the co-editors meet at least every 6 months by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by approvals of new drugs, vaccines, medical devices, or diagnostics; by new information regarding indications or dosing; by new safety or efficacy data; or by other information that may affect prevention and treatment of HIV-related opportunistic infections, including emerging infectious diseases. Updates that may significantly affect patient safety or treatment and that warrant rapid notification may be posted temporarily on the Clinicalinfo website until the guidelines document can be updated. |
| Public Comments | After release of an update on the Clinicalinfo website, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made by the appropriate working group and the co-editors as to whether revisions are indicated. The public may also submit comments to the Panel at any time at HIVinfo@nih.gov. |

# Appendix C. Panel Roster

## Pediatric OI Guidelines Panel

**Updated:** January 09, 2024
**Reviewed:** January 09, 2024

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# Appendix D. Financial Disclosures

**Updated:** January 09, 2024
**Reviewed:** January 09, 2024

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| | | Janssen | Research Support |
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| Brenda Tesini<br>University of Rochester School of Medicine and Dentistry<br>Rochester, NY | Co-author: *Pneumocystis jirovecii* Pneumonia | Merck | Honoraria |
| Jill Weatherhead<br>Baylor College of Medicine<br>Houston, TX | Author: Cryptosporidiosis, Giardiasis, Isosporiasis, Malaria, Microsporidiosis | None | N/A |
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# Appendix E. Archived Sections

## Overview

Following the 2021 Rescoping Consultation of the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV*, several opportunistic infections were identified as either with low frequency in children and prepubertal adolescents with HIV or without HIV-specific management implications. As a result, these sections were recommended not to be further reviewed by the Panel on Opportunistic Infections in Children with and Exposed to HIV (the Panel). The archived sections are Human Herpesvirus 8 Disease, Influenza, and Progressive Multifocal Leukoencephalopathy.

This appendix provides access to the last updated versions of sections that are no longer being reviewed by the Panel.

- Human Herpesvirus 8 Disease
- Influenza
- Progressive Multifocal Leukoencephalopathy

# Human Herpesvirus 8 Disease

**Updated:** December 15, 2016
**Reviewed:** December 15, 2016

| Panel's Recommendations |
| --- |
| I. Is there an indication for serologic testing for human herpesvirus 8 (HHV-8) in asymptomatic HIV-infected children (compared with not testing) to guide clinical management?<br>• Antibody (or DNA testing) for HHV-8 is insufficiently sensitive/specific to predict risk of Kaposi sarcoma. Therefore, routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended (strong, very low).<br>II. Among HIV-infected children, does initiation of antiretroviral therapy (ART) (as compared with non-initiation) reduce the risk of Kaposi sarcoma?<br>• Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated Kaposi sarcoma (strong, low).<br>III. For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of Kaposi sarcoma?<br>• Data are insufficient and conflicting upon which to base a recommendation for a particular ART regimen for prevention of Kaposi sarcoma (weak, low).<br>IV. Among HIV-infected children with active Kaposi sarcoma, is treatment with ART (as compared with no ART) associated with higher rates of remission and/or decreased mortality?<br>• Treatment with ART is associated with increased survival among HIV-infected children with active Kaposi sarcoma. Effective suppression of HIV replication with ART is recommended for all patients with evidence of active Kaposi sarcoma and other HHV-8-associated malignant lymphoproliferative disorders (strong, very low).<br>V. Among HIV-infected children with active Kaposi sarcoma, is treatment with chemotherapy in addition to ART (as compared with ART alone) associated with higher rates of remission and/or decreased mortality?<br>• Systemic chemotherapy, in addition to ART, is associated with higher rates of remission and decreased mortality and is recommended for disseminated or visceral Kaposi sarcoma (stage T1 disease) and for primary effusion lymphoma (strong, low). For localized Kaposi sarcoma (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear.<br>VI. Among HIV-infected children treated with ART who develop immune reconstitution inflammatory syndrome (IRIS), is chemotherapy in addition to continuation of ART (compared with no chemotherapy) associated with higher rates of remission and/or decreased mortality?<br>• For patients with Kaposi-sarcoma-associated IRIS, chemotherapy along with continuation of ART is recommended (strong, low).<br>VII. Among HIV-infected children who achieve remission from Kaposi sarcoma, what therapies are recommended to lower the risk of recurrence?<br>• Effective suppression of HIV replication with ART in HIV-infected patients with Kaposi sarcoma may prevent Kaposi sarcoma progression or occurrence of new lesions and may decrease risk of recurrence after remission. Life-long ART is recommended for all individuals with evidence of active or treated Kaposi sarcoma or other HHV-8-associated malignant lymphoproliferative disorders (strong, low). |
| *Rating System*<br>*Strength of Recommendation: Strong; Weak*<br>*Quality of Evidence: High; Moderate; Low; or Very Low* |

## Introduction/Overview

### *Epidemiology*

Human herpesvirus 8 (HHV-8), also called Kaposi sarcoma (KS)-associated herpesvirus (KSHV), is a gamma human herpesvirus most closely related to Epstein-Barr virus. HHV-8 has been causally linked to all forms of KS (i.e., HIV-related, classic endemic, and iatrogenic) and with two rare neoplastic conditions usually associated with HIV infection: body cavity-based lymphoma, also known as primary effusion lymphoma (a B-cell lymphoma that typically arises in body cavities such as the pleural space), and multicentric Castleman disease (non-cancerous tumors that may develop in lymph nodes in a single site or in multiple sites throughout the body). The exact mechanism by which HHV-8 infection leads to neoplastic disease has not been fully elucidated, but seroconversion to HHV-8 antibody positivity virtually always precedes development of the tumors.[1]

The prevalence of antibodies to HHV-8 varies widely with age, geography, and certain risk factors. In the United States and Europe, 1% to 3% of the general adult population is seropositive, with higher rates (8%) among men who have sex with men (MSM).[2] In a U.S. cohort of HIV-infected and at-risk (but HIV-negative) adolescents with a median age of 19 years, 11.2% were HHV-8 seropositive.[3] The highest rates were in adolescent HIV-infected MSM (23%). Seropositivity was associated with HIV infection, MSM, a history of syphilis, and injection-drug use.[3,4] The general adult seropositivity rate in Mediterranean countries ranges from 10% to 25%. In areas where HHV-8 is endemic, such as eastern and central sub-Saharan Africa, HHV-8 seropositivity rates as high as 80% have been reported in adults.[5-9]

HHV-8 is transmitted through oral and, possibly, genital secretions. Immunocompetent HHV-8-infected adults frequently shed HHV-8 in their oropharyngeal secretions.[10] In areas where HHV-8 infection is endemic, the seroprevalence increases quickly during the first 5 years of life (especially when other family members are HHV-8-positive), then plateaus until adolescence and young adult years.[11,12] The seroprevalence among infants and children increases with the number of HHV-8-positive parents and siblings in the home, indicating non-sexual transmission for prepubertal children, with a limited role for perinatal transmission.[11-18] HHV-8 can also be transmitted through exposure to infected blood, including through intravenous (IV) drug use and blood product transfusions.[19]

For HIV-infected individuals, coinfection with HHV-8 places them at increased risk of KS. Most cases of KS occur in adults (compared with children). Before the advent of antiretroviral therapy (ART), the overall incidence of KS in HIV-infected adults was as high as 20%. However, in the United States and England, KS represented less than 1% of pediatric AIDS-defining illnesses, likely due in part to low HHV-8 seroprevalence in children in these regions. Although KS occurs primarily in adults, the incidence in children has increased dramatically as a result of the HIV pandemic, particularly in sub-Saharan Africa.[20-22] Iatrogenic KS has emerged as well, predominantly among adults in developed settings, with increasing use of immunosuppressive therapies and organ transplantation.[23] Pediatric cases of iatrogenic KS after liver or bone marrow transplantation have also been described.[24-27]

The risk of KS among HIV-infected individuals is highest among those with severe immunodeficiency. KS, primary effusion lymphoma, and multicentric Castleman disease can occur at any CD4 T lymphocyte (CD4) cell count, but they are described most often in HIV-infected patients with more advanced immunosuppression (CD4 cell count <200 cells/mm$^3$ in adults). It should be noted, however, that 5% to 10% of newly diagnosed KS in adults occurs in those with CD4 cell count >300/mm$^3$ and/or low or undetectable plasma HIV RNA levels.[28,29]

The incidence of KS appeared to decline in the United States even before the widespread use of ART. The reason is unclear but may have been related to the use of other antiviral agents, such as those used to treat cytomegalovirus (CMV) (i.e., foscarnet, ganciclovir, and cidofovir), which may inhibit HHV-8.[30-36] The incidence of KS in adults has continued to decrease with the advent of earlier and more aggressive ART.

## *Clinical Manifestations*

Primary infection with HHV-8 in young, immunocompetent children may be asymptomatic or may present as a self-limited mononucleosis-like illness consisting of fever, mild upper respiratory symptoms, and a maculopapular rash. A similar presentation has been described in immunocompetent adults.[37,38] A more severe illness has been described in immunocompromised patients, who may present with disseminated infection with fever, lymphadenopathy, splenomegaly, and pancytopenia.[39,40] Reactivation of HHV-8 has been associated with hemophagocytic lymphohistiocytosis in HIV-infected adults.[41]

KS presentation varies widely, with cutaneous, oral, lymphatic, or visceral involvement, or some combination of the three.[42,43] Pediatric presentations differ from those of adults and are best described in retrospective cohort studies from sub-Saharan Africa.[21,43-45] Cutaneous forms involve characteristic non-tender, purplish, indurated skin lesions, which may be seen in 47% to 83% of affected children. Children also commonly present with lymphatic involvement (30% to 64%), a particularly aggressive form of the disease, and as many as 10% to 18% of these children may not have skin lesions. Intraoral lesions may be seen in 21% to 41%, occasionally (4%) without skin lesions. Visceral dissemination occurs in 12% to 38% of children. Median age at presentation in these studies ranges from 6 years to 10 years, and KS has been diagnosed in children as young as 10 months to 2 years. Median CD4 percentage at presentation in these studies ranges from 7.4% to 16%.

Multicentric Castleman disease presents with generalized adenopathy and fever and may progress to multi-organ failure. Primary effusion lymphoma presents with symptoms related to fluid accumulation in the pleural or pericardial space or with abdominal distention.

## *Diagnosis*

Laboratory diagnosis of HHV-8 infection is most commonly based on serologic assays, such as immunofluorescence, enzyme-linked immunosorbent assay, and Western blot. However, there is no gold standard for diagnosing HHV-8 infection. Serologic tests range in sensitivity from 80% to ≥90% and interassay agreement is poor.[46] Combination assays containing both lytic and late-phase antigens may improve detection rates. Nucleic acid-based tests, such as *in situ* DNA hybridization and polymerase chain reaction (PCR), are important for tissue diagnosis. Although these tests have high levels of sensitivity, their specificity and reproducibility are highly variable. Only 40% to 60% of patients with proven KS will have HHV-8 DNA in their blood or saliva detectable by PCR, and in them, positivity will vary over time.

Diagnosis of KS requires biopsy and histologic examination of affected tissues.

## *Prevention Recommendations*

### Preventing Exposure

Routine testing of children and adults for HHV-8 is not recommended; therefore, the serostatus of HIV-infected patients usually is unknown. Although the efficacy of condoms in preventing HHV-8 exposure has not been established, HIV-infected patients should use male latex condoms correctly and consistently during sexual intercourse to reduce exposure to sexually transmitted pathogens.

### Preventing First Episode of Disease

The use of ART with suppression of HIV replication has markedly decreased the incidence of KS in HIV-infected adults. Several antiviral agents (i.e., ganciclovir, foscarnet, and cidofovir) inhibit HHV-8 replication *in vitro*, and data suggest that their use can prevent KS in patients who are HIV/HHV-8 coinfected.[47] However, antiviral use for prevention of KS is not currently recommended.

## *Treatment Recommendations*

### Treating Disease

Specific treatment regimens are not included in this report because the HIV-related clinical entities associated with HHV-8, such as KS and Castleman disease, are oncologic and traditionally have been treated with cytotoxic chemotherapy. However, in HIV-infected patients with KS, effective suppression of HIV replication with ART may result in improvement in KS lesions, prevent KS progression, or prevent occurrence of new KS lesions. Therefore, ART is recommended for all HIV-infected patients with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders.

In HIV-infected adults with KS, HHV-8 cellular viremia and higher viral load have been associated with disease progression.[48] The vast majority of infected cells are not undergoing lytic replication, and anti-herpesvirus medications have had little or no effect on established KS or HHV-8 cellular viremia. Studies are under way of methods that induce lytic replication or attack the episomal (latent) HHV-8 genome.[49,50]

In contrast to KS, in Castleman disease, many of the cells support lytic replication of HHV-8, and treatment with anti-herpesvirus drugs has led to substantial clinical improvement in some studies.[50] IV ganciclovir or oral valganciclovir may be considered for treating multicentric Castleman disease[51] and may be a useful adjunct for treating primary effusion lymphoma.[52,53] These diagnoses are exceedingly rare in children; in such cases, adult guidelines should be consulted.

### Monitoring and Adverse Events (Including IRIS)

KS-associated immune reconstitution inflammatory syndrome (KS-IRIS) generally describes the appearance of or paradoxical clinical worsening of KS after initiation of a potent ART regimen. KS-IRIS is not predicted by low CD4 cell count.[54] KS-IRIS is associated with higher mortality than KS not associated with IRIS. In African cohorts, where mortality from KS-IRIS is high, chemotherapy in addition to ART was associated with increased survival.[55]

For patients with disease manifestations of HHV-8 infection who are treated with ganciclovir or valganciclovir, refer to the chapter on CMV infections (Monitoring and Adverse Events) for information on treatment-associated adverse events.

### Preventing Recurrence

Effective suppression of HIV replication with ART in HIV-infected patients with KS may result in improvement in KS lesions, prevent KS progression, or prevent occurrence of new KS lesions and is recommended for all individuals with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders.

## *Primary Prevention*

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

Routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended **(strong, very low).**

Although KS is one of the most common cancers in HIV-infected individuals, a minority of coinfected individuals will develop KS. Seroprevalence of HHV-8 varies by country, but in some areas reaches ≥50% by adulthood. Sensitivity and specificity of antibody testing vary, and HHV-8 DNA shedding in saliva and presence in plasma are not consistent. Studies are conflicting on utility of quantitative DNA PCR for prediction of risk of KS in HHV-8-seropositive, HIV-infected adults. Based on lack of accurate prediction of risk of KS by antibody and HHV-8 DNA assays, routine testing is not indicated. For someone known to be HHV-8-seropositive, that factor should be considered in discussions about ART initiation.

### II. Among HIV-infected children, does initiation of ART (as compared with non-initiation) reduce the risk of KS?

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

Multiple observational studies in adults have shown that the incidence of KS is drastically reduced in adults on ART.[56,57] In one retrospective pediatric study, 0 of 1,000 children on ART developed KS, in contrast with 32 children out of 3,000 who presented with or developed KS prior to starting ART.[45]

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

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

Evidence has been conflicting as to whether non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based ART has an advantage in the prevention of KS. Laboratory evidence of PI antitumor activity exists, most notably for nelfinavir, but also for ritonavir and ritonavir-boosted lopinavir. In addition, there is preliminary evidence that PI-based therapy reduces HHV-8 DNA oropharyngeal shedding.[58] One recent, large observational study of adults noted an advantage for PI-based therapy over NNRTI-based regimens in the prevention of KS, but other studies have found no difference between regimens.[56,57] There are no corresponding data from pediatric studies. It should be noted that 5% to 10% of new cases of KS in adults occur in those on therapy, with undetectable viral loads and/or CD4 cell counts >300 cells/mm$^3$.[28,29]

## *Treatment*

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

Effective suppression of HIV replication with ART is recommended for all patients with evidence of active KS and/or other HHV- 8-associated malignant lymphoproliferative disorders **(strong, very low).**

Treatment with ART is first-line therapy against KS and other HHV-8-associated malignant proliferative disorders, and is associated with increased survival among HIV-infected children with active KS.[21,44,58]

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

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

There is a paucity of information to guide the clinical management of HIV-infected children with KS. The available studies were retrospective, had relatively small sample sizes, and were performed in sub-Saharan Africa.[44,45,58] Data from these studies were not adjusted for KS stage or for comorbidities. Additionally, AIDS Clinical Trials Group staging classification has not been validated in children. For focal or early stage KS, HIV-infected adults have been effectively treated with ART alone.[59] Local intralesional chemotherapy or radiation therapy may be considered for focal disease. The available evidence in children suggests that systemic chemotherapy in addition to ART is associated with increased likelihood of remission and decreased mortality. It is unclear, however, if localized disease (stage T0) can be treated effectively without systemic chemotherapy. Data are insufficient on which to base a recommendation for a particular chemotherapy regimen, and various regimens have been used in different settings. Patient clinical presentation and available therapies in the practice setting should be considered, in consultation with an oncologist.

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

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

Studies of HIV-infected adults with KS-associated IRIS (primarily from African cohorts) indicate that chemotherapy in addition to ART, as opposed to ART alone, is associated with reduced mortality.[55,60]

## *Secondary Prevention*

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

Effective suppression of HIV replication with ART in HIV-infected patients with KS may prevent KS progression or occurrence of new lesions and is recommended for all individuals with evidence of active or treated KS and/or other HHV-8-associated malignant lymphoproliferative disorders **(strong, low).**

The risk of KS recurrence has decreased in the ART era. In 1 study of adults treated with pegylated liposomal doxorubicin and ART (which continued after chemotherapy), the relapse rate was 13.5% per year, and was highest in the first year.[61] In 1 large Italian study, a multivariate analysis demonstrated a strong association between use of ART and increased 10-year survival rates after KS.[62]

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# Influenza

**Updated:** July 26, 2018
**Reviewed:** July 26, 2018

| Panel's Recommendations |
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| I. **Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?**<br>• The prevention of influenza in children with HIV aged ≥6 months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) **(strong, moderate)**.<br>• Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccine[a] (e.g., intranasal administered influenza vaccine, FluMist) **(weak, very low)**.<br>• Household members and close contacts (aged ≥6 months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) **(strong, moderate)**. |
| II. **Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?**<br>• Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 T lymphocyte [CD4] cell percentage <15%) while influenza virus is circulating in the community, after careful consideration of risks and benefits as outlined in Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines **(weak, low)**.<br>• Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage <15%), regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza **(strong, moderate)**.<br>• Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable **(strong, moderate)** or in seasons in which low influenza vaccine effectiveness is documented **(strong, low)**, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza. |
| III. **Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?**<br>• Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should be given without waiting for confirmatory laboratory testing and without regard to illness duration **(strong, moderate)**. Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients **(weak, low)**.<br>• Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible **(strong, moderate)**. Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.<br>• In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged >5 years, and has no other underlying condition that places the child at high risk of complications from influenza **(weak, low)**. |

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| *Rating System*<br>*Strength of Recommendation: Strong; Weak*<br>*Quality of Evidence: High; Moderate; Low; or Very Low*<br>[a] *As of the 2017–2018 influenza season, live attenuated influenza vaccine (LAIV)* ***is not recommended*** *by ACIP for any pediatric or adult patient given concerns about effectiveness. Please see the most recent ACIP statements regarding use of LAIV in future seasons.* |

## Epidemiology

Influenza viruses are spread directly from person to person across distances up to 6 feet via large or small droplets generated by coughing or sneezing, or indirectly from contaminated surfaces to hands to mucosal membranes.[1] Influenza has an incubation period of 1 to 4 days (mean: 2 days),[2] and can be shed by adults from 1 day before to 5 to 7 days after onset of symptoms and by children from several days before to ≥10 days after illness onset.[3] Viral shedding can occur over longer periods in those with chronic diseases, including patients with immunosuppression or those receiving systemic corticosteroid therapy.[4-7]

Seasonal influenza viruses can be divided into three types: A, B, and C. Influenza A viruses are further subdivided based on surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Influenza A viruses circulate primarily among aquatic birds, but also among humans and other animals, including pigs, horses, and seals. Influenza A virus subtypes H1N1pdm09 and H3N2 currently circulate among humans. Influenza B viruses circulate primarily among humans.[8] Influenza C viruses circulate primarily among animals such as swine and dogs but are increasingly appreciated in humans.[9-12] Influenza A and B, but not C, cause seasonal outbreaks. Surveillance and immunization are currently performed for influenza A and B. Two influenza A subtypes (one H1N1 and one H3N2); and one influenza B strain for trivalent vaccine formulations, or two influenza B strains for quadrivalent vaccine formulations are included in current seasonal influenza vaccines. In the United States, influenza viruses cause annual outbreaks lasting from winter through spring.

The Centers for Disease Control and Prevention (CDC) has identified certain groups to be at risk of complications from influenza, including individuals with immunosuppression caused by HIV infection.[13] The burden of influenza virus in children with HIV has been characterized in limited case reports and case series, but assessment of its impact has been confounded by the stage of HIV infection, type of antiretroviral therapy (ART), and other comorbidities.[14] In the era before the availability of combination antiretroviral therapy (cART), multiple large epidemiological studies suggested high hospitalization and mortality rates associated with influenza in individuals with HIV.[15,16] However, observations reported during the cART era suggest that better control of HIV infection is associated with a milder course of influenza. In an outbreak of pandemic 2009 H1N1 influenza in Germany involving 15 schoolchildren with HIV receiving cART, the clinical course of influenza in children with HIV was similar to that in children without HIV.[17] A case series of 13 children with HIV with pandemic 2009 H1N1 in Barcelona in 2009 also reported outcomes similar to those in groups without HIV.[18] In both reports, half of the children were aged <13 years, had CD4 T lymphocyte (CD4) counts >500 cells/mm$^3$, and had very low or undetectable HIV viral loads. Recent adult data suggest that, despite the introduction of ART, influenza-related mortality in adults with AIDS is still greater than in the general population.[19] Further, using national mortality and laboratory surveillance data from 1998–2009, a study from South Africa reported that the risk of death associated with influenza in children aged <5 years was greater in children with HIV than in those without HIV (RR 11.5, 95% CI, 9.6–12.6).[20] Large prospective, observational studies of children with HIV are needed to further substantiate these findings.

## Clinical Manifestations

Signs and symptoms related to influenza are similar in children with and without HIV and include fever, cough, and rhinorrhea in the majority of patients.[17,18,21] Loss of appetite was more common in patients with HIV than in patients without HIV in one study.[22] In a prospective cohort study of hospitalized children with laboratory-confirmed influenza conducted in South Africa from 1997 to 1999, prior to cART availability, radiographic evidence of alveolar consolidation was more frequent in children with HIV than in children without HIV. Clinical outcomes including duration of hospitalization and in-hospital mortality were similar for both children with and without HIV.[22] In one small study conducted during the 2009 H1N1 pandemic, chest radiography patterns differed with HIV status; children with HIV were more likely to have an interstitial infiltrate and children without HIV more likely to have a consolidative infiltrate. Children with HIV were also more likely to have leukopenia associated with their influenza diagnosis than children without HIV.[23]

## Diagnosis

The laboratory approach to diagnosis of influenza in children with and without HIV is identical. This includes rapid influenza diagnostic tests (RIDTs), immunofluorescence assays, reverse transcription-polymerase chain reaction (RT-PCR) assays, and viral culture. RT-PCR and viral culture are considered the gold standard influenza tests. Viral culture has lower sensitivity than RT-PCR and results are not immediately available. RIDTs offer point-of-care diagnosis, but sensitivity is substantially lower than for viral culture or RT-PCR, which makes false-negative results a significant concern in clinical application. In addition RIDTs can be falsely positive when the prevalence of influenza is low, thus limiting their reliability for patient management in both high and low prevalence seasons.[24] Clinical diagnosis with laboratory confirmation of influenza is important, especially for hospitalized patients and outpatients at higher risk of influenza complications. Molecular diagnostic methods (e.g., RT-PCR) offer the most sensitive and specific diagnostic testing and can be performed at many specialized laboratories, such as hospital laboratories, commercial referral laboratories, and county and state public health laboratories.

## Prevention Recommendations

### *Preventing Exposure*

Basic personal hygiene, including hand hygiene and proper cough etiquette, are mainstays of influenza prevention. Individuals should avoid touching their eyes, nose, and mouth and avoid contact with sick individuals. Hands should be washed often with soap and water or, if soap and water are unavailable, with an alcohol-based hand rub containing at least 60% alcohol. Proper hand washing technique involves wetting hands with clean running water, applying soap, and rubbing and scrubbing all hand surfaces and under the fingernails for at least 20 seconds. Hands should be dried with a clean towel or air dried. When using alcohol-based hand rub, the hand rub should be applied to one hand, and the hands (including all hand surfaces and fingers) should be rubbed together until dry.

Cough etiquette directs that individuals cough or sneeze into a tissue rather than into their hands. A soiled tissue should be disposed of in a waste basket. Measures used by public health authorities during influenza pandemics include recommendations to reduce crowding, to maintain a few feet of distance from others, to avoid shaking hands or hugging at gatherings, and to avoid gatherings altogether (see Preventing the Flu: Good Health Habits Can Help Stop Germs and Handwashing: Clean Hands Save Lives).

Prolonged influenza viral replication in immunocompromised patients has implications for spread of influenza in the health care setting, as well as in the community. Immunocompromised patients with prolonged viral replication in the respiratory tract could potentially serve as a reservoir for spread of influenza in the hospital and the community. In addition, prolonged viral replication increases the risk for emergence of antiviral resistance if antiviral exposure occurs. Strategies to prevent the spread of influenza in health care facilities include use of standard and droplet precautions by health care workers, as well as caution when performing aerosol-generating procedures according to Healthcare Infection Control Practices Advisory Committee guidelines.[25]

In addition to the above measures, influenza prevention efforts for children with HIV also include vaccinating the children's close contacts and limiting spread of influenza from household members. Household members may be vaccinated with any medically appropriate vaccine formulation. Though not recommended for the 2017–2018 season, live attenuated influenza vaccine (LAIV) is considered safe for household contacts of children with HIV if the contacts fulfill criteria for LAIV receipt. Isolation of household members with any acute respiratory illness from the child with HIV, prompt influenza testing, and presumptive antiviral treatment in potentially infected household members are additional tools to prevent spread of influenza to children with HIV.

## *Preventing First Episode of Disease*

Annual influenza vaccination is a cornerstone of influenza prevention at both the individual and community level.[26] Past concerns about an increase in HIV viral load following influenza vaccination have not been substantiated, particularly in individuals on ART.[13,27-31] Currently in the United States, inactivated influenza vaccine (IIV) is recommended for patients with HIV according to the CDC Advisory Committee on Immunization Practices (ACIP) guidelines. Studies examining the immune response of children and adolescents with HIV on ART to inactivated influenza vaccination have generally shown immune responses comparable to those seen in individuals without HIV.[32] Children with HIV-related immunologic impairment or with symptomatic HIV demonstrate decreased immune responses to influenza vaccination (see Recommendation Table). High-dose IIV was recently studied in a small cohort of children and young adults with HIV, though it was not significantly more immunogenic in these patients than standard-dose IIV.[33] Additional studies of high-dose IIV in populations at increased risk for influenza are in progress. LAIV **is not recommended** for immunosuppressed persons per CDC/ACIP guidance.[34] Furthermore, current Infectious Diseases Society of America (IDSA) guidelines for LAIV immunization of immunocompromised persons state that LAIV **should not be administered** to immunocompromised persons or persons with HIV.[35] Some experts would consider using LAIV (which may remain available) in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV who meet these conditions.[36] However, the CDC/ACIP and IDSA guidelines recommend against such practice, and LAIV is not licensed for use in children with HIV. Further, LAIV is not currently recommended by ACIP for all populations because of decreased effectiveness.

Contraindications to the use of inactivated influenza vaccines are few and are the same for individuals with and without HIV. Influenza vaccines **are not approved** for children aged

<6 months. Per CDC/ACIP guidance, persons with a previous severe allergic reaction to influenza vaccine **should not receive influenza vaccine in the future**.[34] Future avoidance of influenza vaccine in this setting is recommended regardless of the component suspected of being responsible for the reaction. Persons who report having had egg-associated reactions involving symptoms other than hives (e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention, may receive any licensed and recommended influenza vaccine "that is otherwise appropriate for the recipient's age and health status."[34] In persons with severe egg reactions, influenza vaccine should be administered in an inpatient or outpatient medical setting with supervision by a health care provider able to recognize and manage severe allergic conditions.[34] A physician should be consulted before influenza vaccine is administered to children who have a moderate-to-severe illness with a fever (in which case, vaccination should be postponed until the child recovers).

Options for antiviral chemoprophylaxis of influenza include antiviral administration in the pre- or post-exposure setting to children and adolescents with HIV (see Panel Recommendations above). Pre-exposure prophylaxis should rarely be used, except in persons who are severely immunocompromised and therefore at very high risk for influenza virus-associated morbidity and mortality during periods of greatly increased risk for influenza exposure.[37] The choice to provide post-exposure prophylaxis to an individual patient depends on the patient's state of immunosuppression and immunization status, as well as the seasonal vaccine effectiveness depending on the vaccine match with the circulating strains of influenza (See Panel Recommendations above and Evidence Summary below).[37] Selection of an antiviral drug for chemoprophylaxis should be based on current CDC/ACIP influenza antiviral recommendations and take into consideration the weekly antiviral susceptibility testing data for the circulating influenza virus strains that is provided by CDC (see Weekly U.S. Influenza Surveillance Report or FluView). Post-exposure antiviral chemoprophylaxis should be started within 48 hours of exposure to a contact with confirmed or suspected influenza. Oseltamivir and zanamivir, which are members of the antiviral class of medications called neuraminidase inhibitors, are approved and are recommended for chemoprophylaxis against influenza A and B viruses in children. Oseltamivir prophylaxis is not Food and Drug Administration (FDA)-approved for children aged <1 year, but the American Academy of Pediatrics (AAP) and CDC have issued recommendations for prophylaxis of children aged ≥3 months; zanamivir prophylaxis is not recommended for children aged <5 years (see table below). Although oseltamivir resistance has been documented previously among circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) circulating influenza A and B viruses have been susceptible to oseltamivir.[37,38] Amantadine and rimantadine, adamantane derivatives which only have activity against influenza A viruses, are approved but not currently recommended for chemoprophylaxis of influenza A virus infection because of widespread resistance of current influenza A (H3N2 and H1N1pdm09) virus strains to adamantanes.[37,39]

## *Discontinuing Primary Prophylaxis*

Though used only rarely, when a pre-exposure chemoprophylaxis strategy is employed, antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community.[37]

The recommended duration of post-exposure chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child's degree of immunosuppression and the degree of match with circulating influenza viruses.[37,40] If influenza vaccination is provided after contact, chemoprophylaxis duration should generally be 2 weeks after vaccination. If exposure is to a household contact, chemoprophylaxis duration should be 7 days (see Influenza Antiviral Medications: Summary for Clinicians). If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days, or 7 days after onset of symptoms in the last person infected, whichever is longer. The duration of chemoprophylaxis after other exposure types should generally be 7 days.

## Treatment Recommendations

### *Treating Disease*

Treatment of influenza in children with HIV is recommended according to CDC/ACIP guidelines. The recommended duration of treatment is 5 days, but may need to be extended in severely ill hospitalized or immunocompromised patients.[40-43] As with primary chemoprophylaxis, selection of an antiviral drug for treatment should be based on current CDC/ACIP influenza antiviral recommendations and should account for antiviral susceptibility testing data for circulating influenza virus strains that is provided by CDC (see Weekly U.S. Influenza Surveillance Report or FluView). Currently recommended influenza antiviral medications are the neuraminidase inhibitor drugs, oseltamivir (orally administered), zanamivir (inhaled), and peramivir (intravenous). Peramivir is approved for treatment in persons aged ≥18 years. All three are effective for treatment against influenza A and B viruses. Oseltamivir is FDA-approved for treatment of influenza in children aged ≥2 weeks; however, both CDC and AAP recommend the use of oral oseltamivir for treatment of influenza in infants aged <2 weeks when needed (see Influenza Antiviral Medications: Summary for Clinicians).[43]

Although oseltamivir resistance was documented in circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) of circulating influenza A and B viruses have been susceptible to oseltamivir.[37,38] Zanamivir is approved for treatment of influenza in children aged ≥7 years (see Table below). Peramivir, though FDA-approved only for treatment of persons aged ≥18 years, has been studied in pediatric populations.[44-46] Importantly, the most common neuraminidase inhibitor mutation (H275Y) imparts resistance to both oseltamivir and peramivir.[47,48] Adamantanes (rimantadine, amantadine) have activity only against influenza A viruses, but are not currently recommended for treatment of influenza A because of resistance of currently circulating influenza A (H3N2 and H1N1pdm09 virus strains).[37,39]

### *Monitoring of Adverse Events*

Clinicians should take into account patients' age, weight, renal function, history of seizures, level of immunosuppression, other medical conditions, and potential drug interactions when considering administration of influenza antiviral medications and evaluating their associated adverse events.[37]

#### Oseltamivir

In studies in adults and children, mild nausea and vomiting have been the most common side effects of treatment with oseltamivir;[49,50] however, these symptoms can be reduced if the medication is taken with food.[51] Despite earlier post-market reports from Japan of transient neuropsychiatric events manifested as self-injury or delirium, oseltamivir has not been reproducibly associated with increased risk of neuropsychiatric events.[52] Moreover, influenza infection itself is associated with neurologic complications such as febrile seizures, encephalopathy, and encephalitis. FDA recommends close monitoring for abnormal behavior in patients treated with oseltamivir.[51] FDA and CDC also recommend that clinicians and pharmacists pay careful attention to avoid dosing errors in young children.[53]

### Zanamivir

Because of cases of respiratory deterioration manifested as decreased forced expiratory volume or bronchospasm in patients with asthma or chronic obstructive pulmonary disease receiving zanamivir, this agent **is not recommended** for treatment of influenza in patients with underling pulmonary disease. In clinical treatment studies involving patients with uncomplicated influenza, common adverse events were similar in those treated with inhaled zanamivir and those treated with inhaled placebo.[37,41]

### Drug Interactions

Clinical data are limited with respect to drug interactions between influenza antiviral drugs and antiretroviral (ARV) drugs, and no clinical trials to date have evaluated the safety or efficacy of using combinations of different classes of influenza antiviral drugs.[37] However, information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions with ARV agents are unlikely. Moreover, since none of the neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) affect cytochrome P450 (CYP450) isoenzymes, no clinically significant drug interactions are predicted based on *in vitro* studies.

## *Managing Treatment Failure (Influenza Disease Progression)*

Clinicians developing management plans in response to treatment failure or severe illness associated with influenza viral infections can consider changing antiviral dosing or route of administration, increasing duration of therapy, or tailoring therapy based on viral resistance.[40] The potential use of increased oseltamivir doses in critically ill patients has emerged from concerns surrounding enteric absorption of oseltamivir in this patient population, but these concerns have not been substantiated in clinical trials. One small study demonstrated therapeutic plasma levels of oseltamivir in critically ill adult patients comparable to those seen in ambulatory adult patients.[54] In addition, a prospective study from Hong Kong showed no overall clinical or virologic benefit of higher dose as compared to standard dose oseltamivir in hospitalized adults, though a trend to more rapid viral clearance of influenza B, but not of influenza A, was noted in a sub-analysis.[55] Patients who are severely ill and hospitalized or who are immunosuppressed may require longer treatment with oseltamivir.[40] For hospitalized children or those with severe disease, treatment with inhaled zanamivir is not recommended because evidence for its use in this setting is lacking. In December 2014, FDA approved intravenous (IV) peramivir for treatment of acute uncomplicated influenza in persons aged ≥18 years. Although not licensed for children, pediatric use of peramivir is reported and off-label use could be considered in severely ill children, especially those patients who cannot tolerate or absorb oral/enteral oseltamivir. Expert opinion supports consideration of IV peramivir use in hospitalized children aged ≥2 years and adults or those with severe disease, although efficacy in this setting has not been demonstrated.[40,44] Further studies to support its safety and efficacy are needed.[45,56,57]

Prior to the 2017–2018 influenza season, IV zanamivir was available through clinical trial enrollment or via an Emergency Investigational New Drug application for settings in which oseltamivir-resistant influenza virus infection was suspected or confirmed (see Influenza Antiviral Medications: Summary for Clinicians). However, at present IV zanamivir is no longer available in the United States.

Importantly, as noted above, if oseltamivir-resistant influenza virus infection is suspected or confirmed, peramivir is not indicated because of demonstrated cross-resistance between oseltamivir and peramivir.

### Preventing Recurrence

See sections Preventing Exposure and Preventing First Episode of Disease.

### Discontinuing Secondary Prophylaxis

Not applicable.

## Primary Prevention

### *1. Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?*

i. Prevention of influenza in children with HIV aged ≥6 months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) **(strong, moderate).** This recommendation is based on review of IDSA,[35] CDC/ACIP,[34] and AAP[43] guidelines.

   Annual influenza vaccination is universally recommended for all children aged ≥6 months.[34] Studies of influenza vaccination in children with HIV have generally shown that influenza vaccination is safe and immunogenic. Some studies have demonstrated that, compared to children without HIV, children with HIV have decreased antibody responses to influenza vaccination.[58,59,60,61] Others have shown that children with HIV with greater immune impairment or a more symptomatic clinical stage had decreased immune response to influenza vaccination.[62,63] Despite this potential for modestly impaired immune response to influenza vaccination in children with HIV, seroprotection (i.e., hemagglutination inhibition [HAI] antibody titer ≥1:40) was achieved in up to 92% of vaccine recipients[64] and seroconversion (≥4-fold rise in post-vaccine HAI titer as compared to pre-vaccine HAI titer) in as many as 85% of vaccine recipients[65] in studies of children with HIV.

   In one randomized, double-blind, placebo controlled trial of influenza vaccination in children with HIV, immune responses were measured by HAI and vaccine efficacy was determined using active surveillance data.[66] Seroprotection among the vaccinated population was low and vaccine efficacy was only 17.7% (95% CI, 0% to 62.5%). Importantly, 92% of participants in this study were receiving ART and the median CD4 percentage was 33.5 (range: 15.2% to 55.9%). However, in a similar study performed in adults with HIV in the same setting, vaccine efficacy was 75.5% (95% CI, 9.2% to 95.6%).[67] Thus, given the CDC/ACIP recommendation for universal influenza vaccination in children aged ≥6 months and the potential for protection against influenza by administration of influenza vaccination, yearly administration of influenza vaccine to children with HIV is strongly advised.

ii. Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccines (intranasal administered influenza vaccine, FluMist) **(weak, very low).** This recommendation is based on review of the IDSA guideline for vaccination in the immunocompromised host.[35]

Several studies have evaluated LAIV administration to children and/or adults with HIV.[68,36,69,60,70] In these studies, LAIV administration was safe and not associated with serious adverse events. In most of these studies, individuals with HIV were not significantly immunocompromised at the time of study vaccination. Although some experts would consider using LAIV in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV meeting these conditions,[36] current IDSA guidelines for immunization of immunocompromised hosts recommend against immunization of children, adolescents, and adults with HIV with LAIV.[35]

iii. Household members and close contacts (aged ≥6 months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) **(strong, moderate).**

Annual influenza vaccination is universally recommended for all adults and children aged ≥6 months.[34,71] Given the immunocompromised state of children with HIV and the potential for impaired immune response to influenza vaccination, special emphasis on vaccination of those persons in household and/or close contact with children with HIV is warranted. Ensuring that household/close contacts are vaccinated against influenza likely provides additional prevention against influenza in children with HIV. While there are no specific studies addressing a “cocoon” strategy for influenza prevention in children with HIV, this recommendation is in accordance with universal influenza vaccination recommended by CDC/ACIP.

### 2. *Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?*

i. Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 percentage <15%) while influenza virus is circulating in the community **(weak, low).** Use of this strategy requires careful consideration of risks and benefits and attention to influenza circulation as outlined in CDC/ACIP,[37] IDSA,[42] and AAP[43] guidelines.

ii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage <15%) regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza **(strong, moderate).**

iii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable **(strong, moderate)** or in seasons in which low influenza vaccine effectiveness is documented **(strong, low)** if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.

No antiviral chemoprophylaxis studies for prevention of influenza have been specifically performed in children with HIV. These recommendations were made with reference to current guidelines on antiviral chemoprophylaxis against influenza published by the CDC/ACIP, IDSA, and AAP. In severely immunosuppressed children, influenza vaccination may be poorly immunogenic. Therefore, antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression regardless of vaccination status.

Post-exposure antiviral chemoprophylaxis should be given **only** if it can be started within 48 hours after the initial exposure **and** if the recipient is asymptomatic. If more than 48 hours have elapsed since the initial exposure, then either no chemoprophylaxis should be given, or the treatment antiviral dose should be given. If the potential recipient is already symptomatic, prompt antiviral treatment should be initiated (see Clinical Question #3). Use of prophylactic once-daily dosing in the setting of active viral replication poses a risk of emergence of antiviral resistance.[72-75] Further information regarding antiviral chemoprophylaxis can be found at Influenza Antiviral Medications: Summary for Clinicians.

## Treatment

### *3. Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?*

i. Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should be given without waiting for confirmatory laboratory testing and without regard to illness duration **(strong, moderate).** Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients **(weak, low).**

ii. Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible **(strong, moderate).** Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.

iii. In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged >5 years, and has no other underlying condition that places the child at high risk of complications from influenza **(weak, low).**

No antiviral treatment studies have been specifically performed in children with HIV with influenza. The recommendations are made with reference to current influenza chemoprophylaxis and treatment guidelines published by CDC/ACIP,[37] IDSA,[42] and AAP.[43] Further information regarding antiviral treatment can be found at Influenza Antiviral Medications: Summary for Clinicians.

## Secondary Prevention

Not applicable.

## Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza

| Indication | First Choice | Alternative | Comments/Special Issues |
|---|---|---|---|
| Primary Chemoprophylaxis (Pre- and Post-Exposure)<br><br>Influenza A and B | Oseltamivir<br>• Aged <3 Months: Not recommended[a]<br>• Aged 3 Months to <1 Year: Oseltamivir 3mg/kg body weight/dose once daily[a]<br>• Aged ≥1 to 12 Years: Weight-band dosing[a]<br>  o Weighing ≤15 kg: Oseltamivir 30 mg once daily<br>  o Weighing >15 kg to 23 kg: Oseltamivir 45 mg once daily<br>  o Weighing >23 kg to 40 kg: Oseltamivir 60 mg once daily<br>  o Weighing >40 kg: Oseltamivir 75 mg once daily<br>• Aged ≥13 Years: Oseltamivir 75 mg once daily<br><br>Zanamivir (Aged ≥5 Years)<br>• Zanamivir 10 mg (2 inhalations) once daily[b] | None | Pre-Exposure Chemoprophylaxis<br>*Indications*<br>• After careful consideration of risks and benefits, pre-exposure antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression while influenza virus is circulating in the community.<br>*Duration*<br>• When employed, pre-exposure antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community.<br><br>Post-Exposure Chemoprophylaxis<br>*Indications Recommended For:*<br>• Children with HIV with severe immunosuppression regardless of influenza vaccination status.<br>• Children with HIV with moderate to no immunosuppression if<br>  o Influenza vaccination is contraindicated or unavailable; *or*<br>  o Low influenza vaccine effectiveness is documented in the current influenza season; *and*<br>  o Antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.<br>*Duration*<br>Note: Duration of chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child's degree of immunosuppression and the degree of match with circulating influenza viruses.<br>• If influenza vaccination is provided after contact, chemoprophylaxis duration should be 2 weeks after vaccination. |

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| | | | • If exposure is to a household contact, chemoprophylaxis duration should be 7 days.<br>• If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days or 7 days after onset of symptoms in the last person infected, whichever is longer.[c]<br>Oseltamivir Dosing Adjustments<br>*Premature Infants*<br>• Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).[d]<br>*Renal Insufficiency*<br>• A reduction in dose of oseltamivir is recommended for patients with CrCl <30 mL/min. For patients with CrCl 10–30mL/min, a reduction in chemoprophylaxis dosing frequency to every other day is recommended. Pharmacokinetic data are limited for dosing recommendations for patients with severe renal insufficiency on dialysis. |
| Secondary Chemoprophylaxis | N/A | N/A | No role for secondary chemoprophylaxis |
| Treatment<br>Influenza A and B | Oseltamivir[e]<br>• Aged <3 Months: Oseltamivir 3mg/kg/dose twice daily<br>• Aged 3 Months to <1 Year: Oseltamivir 3 mg/kg/dose twice daily<br>• Aged ≥1 to 12 Years: Weight-band dosing<br>o Weighing ≤15 kg: Oseltamivir 30 mg twice daily<br>o Weighing >15 kg to 23 kg: Oseltamivir 45 mg twice daily<br>o Weighing >23 kg to 40 kg: Oseltamivir 60 mg twice daily | None | *Duration*<br>• The recommended antiviral treatment duration for either oseltamivir or zanamivir is 5 days. Per CDC recommendations, longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.[c]<br>Oseltamivir Dosing Adjustments<br>*Premature Infants*<br>• Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).[d]<br>*Renal Insufficiency*<br>• Oseltamivir renal dosing is not well established for pediatric patients. For children >40 kg, adult renal dosing can be used. |

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| | o Weighing >40 kg: Oseltamivir 75 mg twice daily<br>• Aged ≥13 Years: Oseltamivir 75 mg twice daily<br>Zanamivir (Aged ≥7 Years)<br>• Zanamivir 10 mg (2 inhalations) twice daily[f] | | CrCl/Dose<br>• 61–90 mL/minute: 75 mg twice daily<br>• 31–60 mL/minute: 30 mg twice daily<br>• 11–30 mL/minute: 30 mg once daily<br>• ≤10 mL/minute, ESRD on hemodialysis: 30 mg dose after every hemodialysis cycle<br>• ≤10 mL/minute, ESRD continuous ambulatory peritoneal dialysis: single 30 mg dose administered after a dialysis exchange |

[a] Oseltamivir is FDA-approved for prophylaxis of influenza in children aged ≥1 year. It is not approved for prophylaxis in children aged <1 year. However, CDC recommends that health care providers who treat children aged ≥3 months to <1 year administer a chemoprophylaxis dose of oseltamivir 3 mg/kg body weight/dose once daily. Chemoprophylaxis for infants aged <3 months **is not recommended** unless the exposure situation is judged to be critical.

[b] Zanamivir **is not recommended** for chemoprophylaxis in children aged <5 years or for children with underlying respiratory disease.

[c] See Fiore 2011 and Influenza Antiviral Medications: Summary for Clinicians for further details.

[d] See Acosta et al. *J Infect Dis* 2010; 202:563-566 for dosing recommendations in premature infants.

[e] Oseltamivir is FDA-approved for treatment of influenza in children aged ≥2 weeks; however, both CDC and AAP recommend use of oral oseltamivir for influenza treatment in infants aged <2 weeks.

[f] Zanamivir **is not recommended** for treatment in children aged <7 years or for children with underlying respiratory disease.

**Key:** AAP = American Academy of Pediatrics; CDC = Centers for Disease Control and Prevention; CrCl = creatinine clearance; ESRD = end stage renal disease; FDA = Food and Drug Administration; PK = pharmacokinetic

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# Progressive Multifocal Leukoencephalopathy

**Updated:** October 6, 2013
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| Panel's Recommendations |
|---|
| • The main approach to treatment of Progressive Multifocal Leukoencephalopathy (PML) is treatment with an effective antiretroviral regimen that suppresses HIV viremia and preserves or restores CD4 T lymphocyte (CD4) cell-defined immune function (**AII**).<br>• Intrathecal cytosine arabinoside and cidofovir are not routinely recommended for treatment of PML (**BIII**).<br>• Immunomodulatory approaches, such as interferon alfa, are not routinely recommended for treatment of PML (**BIII**). |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>[†]*Studies that include children or children/adolescents, but not studies limited to post pubertal adolescents* |

## Epidemiology

First described in association with disorders of B-cell function, such as chronic lymphocytic leukemia and Hodgkin disease, progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS) that occurs in immunocompromised patients.[1] In HIV-infected adults, CD4 T lymphocyte (CD4 cell) counts less than 100 cells/mm$^3$ are associated with development of PML, and persistence of CD4 counts less than 50 to 100 cells/mm$^3$ are associated with fatal PML. Not all patients with PML have severe immune dysfunction, however, and PML has been reported in HIV-infected patients with high CD4 counts who are receiving successful combination antiretroviral therapy (cART).

PML is caused by JC virus (JCV), a ubiquitous polyomavirus, named using the initials of the patient, John Cunningham, from whom it was first isolated. Most humans are infected with JCV early in life; in a seroepidemiology study, 50% of Swedish children were seropositive for JCV by ages 9 to 11 years, and 72% of adult women aged ≥25 years in the Finnish Maternity Cohort were JCV seropositive.[2] The exact mode of transmission of JCV between individuals is unknown. Because the virus is commonly detected in urine, JCV has been detected in sewage effluent. It is also detectable in peripheral blood mononuclear cells of both healthy and immunocompromised individuals. Vertical transmission from mother to newborn also has been documented.[3, 4] Lymphocytes, renal tubular epithelium, bone marrow, and possibly spleen and lymphoid tissue likely represent sites of viral latency, and lymphocytes also may be a vehicle for spread of the virus to other organ systems, including the CNS.[5, 6]

The evolution of asymptomatic infection with JCV to symptomatic PML probably involves a series of events that are both virologic and immunologic. The original infecting strain of JCV—the strain that is commonly detected in urine and blood—mutates and alters a regulatory gene through rearrangement of a non-coding region (at-NCCR to rr-NCCR) to become a neurotropic strain of JCV capable of replicating in neuronal glial cells.[7] Failed immune surveillance allows replicating virus to persist in peripheral blood cells and serum. If the neurotropic form of JCV gains entry into the brain, it can then establish a productive infection in oligodendrocyte cells, which leads to PML in the absence of proper CNS immune surveillance.[8] Serotonin receptor 5-HT(2a) appears important for JCV infection of brain glial cells.[9] Recently, in HIV-uninfected adults, an increased incidence of PML has been associated with use of therapeutic monoclonal antibodies, including natalizumab (an alpha 4 beta 1 and alpha 4 beta 7 antagonist that targets activated lymphocytes), efalizumab (an anti CD-11a antibody that targets T-lymphocytes), rituximab (an anti CD-20 antibody that targets B-lymphocytes), and alemtuzumab (an anti-CD52 antibody that depletes both T and B cells).[8, 10-12]

PML is an AIDS-defining illness in HIV-infected individuals. It has rarely been seen in reports from large series of HIV-infected children,[13-15] but cases have been reported in children with a wide range of ages and a broad geographical distribution.[16-22] The incidence of PML has decreased from 3.3 cases per 1000 person-years at risk during the era before cART, to 1.3 cases per 1000 person-years after the introduction of cART.[23] During the pre-cART era, survival was extremely poor in adults and children with PML.[15] Survival among adults has improved during the cART era[24-26] from 10% to 50%, and mean survival time from time of diagnosis of PML has increased from 0.4 years to 1.8 years.[27] No comparable data exist for children.

## Clinical Manifestations

No symptoms are known to be associated with acute or latent JCV infection. Asymptomatic urinary shedding is common. PML is the primary disease caused by JCV and clinical manifestations in children are similar to those in adults. The disease has an insidious onset and produces a neurologic syndrome that steadily progresses over weeks or months, characterized by confusion, disorientation, lack of energy, loss of balance, cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, visual abnormalities (blurred or double vision or loss of vision), hemiparesis or quadriparesis, and eventually coma.

Demyelination is at first patchy, involving subcortical regions, and then spreads to deep white matter in a confluent pattern; thus, PML initially may present with focal neurologic deficits that involve different brain regions.

## Diagnosis

The established criteria for clinical diagnosis are focal signs and symptoms on neurologic examination, focal white matter lesions on magnetic resonance imaging (MRI) or computerized tomography (CT) without mass effect, and exclusion of other causes of the clinical and neuroradiologic findings.[28] A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings, coupled with brain biopsy demonstrating a characteristic triad of pathologic foci of demyelination, enlarged hyperchromatic oligodendrocytes with enlarged nuclei and basophilic-staining intranuclear material, and enlarged astrocytes with bizarre hyperchromatic nuclei. When only two of these features are present, JCV can be demonstrated by *in situ* hybridization or by electron microscopy for definitive diagnosis.

Brain biopsy remains the gold standard confirmatory test for diagnosis of PML, but brain imaging with MRI or CT can reveal characteristic lesions. The radiologic features of PML are typically non-inflammatory (unless associated with immune reconstitution inflammatory syndrome [IRIS] related to initiation of cART). Typical CT abnormalities include single or multiple hypodense, non-enhancing cerebral white matter lesions; cerebellum and brain stem occasionally are involved. MRI may be more sensitive for detecting changes in the brain associated with PML, and may be positive before JCV DNA is detected in the cerebrospinal fluid (CSF). MRI depicts white matter lesions of low T1 signal intensity and high proton density on T2-weighted images with absence of edema or mass effect. Post-contrast enhancement is unusual, and when present, usually is sparse, with a thin or reticulated appearance adjacent to the edge of the lesions.

PML diagnosis is now facilitated by use of a polymerase chain reaction (PCR) assay to detect JCV DNA in CSF, which may obviate the need for brain biopsy in patients with a compatible clinical syndrome and radiographic findings. Nested JCV DNA PCR on CSF is highly sensitive (90%–100%) and specific (92%–100%) for PML in adults, and in the absence of comparative data for children, similar performance characteristics are anticipated but not proven in that population.[29] False-negative tests occur, however, and PML may be present and diagnosed by brain biopsy in patients with a negative JCV DNA PCR test in the CSF. Measurement of JCV DNA levels in CSF samples can be a useful virologic marker for managing PML in patients receiving cART.[30] With the advent of multiple modalities to support PML diagnosis, diagnostic criteria can be stratified according to the following terminology and levels of certainty of diagnosis:

- **Biopsy-confirmed PML:** JCV antigens detected by immunohistochemistry, JCV DNA detected by *in situ* nucleic acid hybridization, or JC virions detected by electron microscopy in brain tissue obtained by cerebral biopsy, associated with typical histology, in patients with typical clinical and radiological findings
- **Laboratory-confirmed PML:** JCV DNA detected by PCR of CSF in patients with typical, clinical, and radiological findings (detection of intrathecal antibody production may also support the diagnosis)
- **Possible PML:** Patients with typical clinical and radiological findings, without virologic or histologic confirmation in brain tissue or CSF.[31, 32]

Presence of antibodies to JCV in the serum or presence of JCV DNA in the blood or urine of patients does not establish the diagnosis of PML because these studies can be positive in individuals without PML. Conversely, while most patients with JCV-associated PML have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF, some patients with PML diagnosed by brain biopsy will not have detectable anti-JCV antibody or JCV DNA in their blood or CSF. Most patients with JCV-associated PML, however, have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF.

## Prevention Recommendations

### *Preventing Exposure*

There is no known way to prevent exposure to JCV.

### *Preventing First Episode of Disease*

Use of cART can prevent or reverse the severe immunosuppression that increases the risk of PML. Incidence of PML has decreased in the cART era. There are no means of preventing PML in severely immunosuppressed individuals.

### *Discontinuing Primary Prophylaxis*

No means of primary prophylaxis of JCV infection or development of PML have been demonstrated.

## Treatment Recommendations

### *Treating Disease*

No effective specific therapy has been established for JCV infection or PML. Survival in HIV-infected adults with PML has substantially improved during the post-cART era, with an increase in median survival from 14 to 64 weeks.[27, 33] A CD4 count >100 cells/mm$^3$ at PML diagnosis is associated with improved survival, and use of cART after diagnosis of PML is strongly associated with improved survival.[33] Thus, the main approach to treatment involves optimizing cART to reverse the immunosuppression that interferes with normal host response to this virus **(AII).**

A number of agents have been proposed or reported anecdotally as more specific treatments for PML, but none has proven effective after greater scrutiny or more extensive study. In a randomized, open-label trial of intravenous (IV) and intrathecal cytosine arabinoside[34] and a non-randomized, open-label trial of IV cidofovir,[35] neither drug was effective in producing clinical improvement of PML in HIV-infected adults, and neither agent is routinely recommended **(BIII).** Immunomodulatory approaches such as interferon-alfa (IFN-α) also have been described in case reports in HIV-infected adults; however, none have been studied in a controlled clinical trial and, in one analysis, these approaches did not provide any benefit beyond that with cART.[36] Thus, they are also not routinely recommended **(BIII).** Anecdotal reports have been published about use of mirtazapine (a 5-HT(2a) receptor antagonist) plus either cidofovir or cytosine-arabinoside, with tapering of immunosuppressive therapy, to treat PML in HIV-uninfected adults who developed the disease while on immunosuppressive therapy. While the results with this adjunctive treatment are encouraging, there is insufficient evidence to recommend it at this time.[31, 37, 38] In addition, recent *in vitro* studies have shown that CMX001, an investigational oral ester form of cidofovir, suppresses JCV replication in human brain cell cultures, and the compound may be evaluated in clinical trials in the near future.[39, 40] No therapeutic trials have been conducted in children.

### *Monitoring and Adverse Events, Including IRIS*

Patients may develop PML before starting cART or may manifest PML as an unmasking IRIS event after immune reconstitution with antiretroviral therapy (ART). Neurologic stability or improvement and prolonged survival are associated with reduced levels of JCV DNA in CSF, appearance of JCV-specific antibody in CSF, and presence of JCV-specific cytotoxic T-cell responses in patients receiving cART.[41]

After cART is initiated and CD4 counts rise, some patients will experience neurologic improvement; however, reports have documented worsening neurologic manifestations after initiation of ART.[26] Clinical worsening may represent the natural history of PML in these patients. However, this apparent worsening may also be a paradoxical reaction from inflammatory responses to JCV potentiated by cART-induced immune reconstitution, called IRIS,[26, 42-44] examples of which have occurred in children.[45] The underlying mechanism of cART-associated PML IRIS is controversial. One hypothesis is that a reduction in inhibitory cytokines (e.g., IFN-α and interleukin-12) after cART promotes JCV re-activation within the brain or increases trafficking of JCV-infected peripheral lymphocytes into the brain.[46] Another possibility is that JCV infection occurring coincidental to cART initiation results in a beneficial inflammatory response, with lack of disease progression.[46] This may be particularly likely in cases of perinatal HIV infection, because JCV acquisition is most common early in life. The overall prevalence of PML-associated IRIS in children is unknown. Inflammatory PML should be suspected in cART-treated children with advanced HIV who show acute neurologic deterioration and contrast-enhancing demyelinating lesions on MRI, even if immunological and virological measures show improvement in HIV status.[22] Retrospective data suggest that early and prolonged treatment with steroids may be beneficial for some patients in whom immune reconstitution with ART activates an inflammatory response to JCV. No clinical trial data exist, however, to substantiate the anecdotal evidence.[47]

### *Managing Treatment Failure*

PML remission with cART may take several weeks, and no criteria exist that define progression of disease. A working definition of treatment failure used for HIV-infected adults is continued clinical worsening and continued detection of CSF JCV DNA at 3 months (see *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults*).[48] In addition, lack of JCV antibody response or JCV-specific cytotoxic T-cell immune responses are associated with poor prognosis. In some patients, PML worsens despite cART, either because of IRIS or because of the natural history of PML. Whichever is the case, cART should be continued. If cART fails to suppress HIV RNA or to increase the CD4 count, then attention should focus on modifying and optimizing the cART **(AII).** In HIV-infected children responding well to cART but with continued worsening of PML, an expert in pediatric HIV infection should be consulted for consideration of investigational therapies.

### *Preventing Recurrence*

On the basis of its role in reversing the disease, the main measure for preventing PML recurrence is an effective cART regimen that suppresses HIV viremia and preserves or restores CD4-defined immune function **(AII).**

### *Discontinuing Secondary Prophylaxis*

No methods for secondary prophylaxis of JCV infection or PML have been proven effective.

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## Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

Updated: September 14, 2023
Reviewed: September 14, 2023

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Bacterial Infections<br>(*S. pneumoniae* and other invasive bacteria) | • Pneumococcal, Meningococcal, and Hib vaccines<br>• Intravenous immune globulin (400 mg/kg body weight every 2 to 4 weeks) | TMP-SMX, 75/375 mg/m$^2$ body surface area per dose by mouth twice daily | See Figures 1 and 2 for detailed vaccines recommendations.<br>Vaccines Routinely Recommended for Primary Prophylaxis. Additional Primary Prophylaxis Indicated for—<br>• Hypogammaglobulinemia (that is, IgG <400 mg/dL)<br>Criteria for Discontinuing Primary Prophylaxis<br>• Resolution of hypogammaglobulinemia<br>Criteria for Restarting Primary Prophylaxis<br>• Relapse of hypogammaglobulinemia | November 6, 2013 |
| Candidiasis | Not routinely recommended | N/A | N/A | January 31, 2019 |
| Coccidioidomycosis | N/A | N/A | Primary prophylaxis not routinely indicated in children. | November 6, 2013 |
| Cryptococcosis | Not recommended | Not recommended | N/A | November 6, 2013 |
| Cryptosporidiosis | ARV therapy to avoid advanced immune deficiency | N/A | N/A | August 29, 2019 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Cytomegalovirus (CMV) | • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food<br>• For children aged 4 months to 16 years, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 x BSA x CrCl (up to maximum CrCl of 150 mL/min/1.73 $m^2$) orally once daily with food (maximum dose 900 mg/day) | N/A | Primary Prophylaxis Can Be Considered for—<br>• CMV antibody positivity and severe immunosuppression (i.e., CD4 count <50 cells/$mm^3$ in children age ≥6 years; CD4 percentage <5% in children age <6 years).<br>Criteria for Discontinuing Primary Prophylaxis<br>• Age ≥6 years with CD4 count >100 cells/$mm^3$<br>• Age <6 years with CD4 percentage >10%<br>Criteria for Considering Restarting Primary Prophylaxis<br>• Age ≥6 years with CD4 count <50 cells/$mm^3$<br>• Age <6 years with CD4 percentage <5% | August 3, 2023 |
| Giardiasis | ART to avoid advanced immunodeficiency | N/A | N/A | August 22, 2019 |
| Hepatitis B Virus (HBV) | • Hepatitis B vaccine<br>• Combination of hepatitis B immunoglobulin and hepatitis B vaccine to infants born to mothers with hepatitis B infection | Hepatitis B immunoglobulin following exposure | See Figures 1 and 2 for detailed vaccine recommendations.<br>Primary Prophylaxis Indicated for—<br>• All individuals who are not HBV infected<br>Criteria for Discontinuing Primary Prophylaxis<br>• N/A<br>Criteria for Restarting Primary Prophylaxis<br>• N/A | November 6, 2013 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Hepatitis C Virus (HCV) | None | N/A | N/A | November 6, 2013 |
| Herpes Simplex Virus Infections (HSV) | N/A | N/A | Primary prophylaxis not indicated | November 6, 2013 |
| Histoplasmosis | N/A | N/A | Primary Prophylaxis Indicated for—<br>• Selected HIV-infected adults but not children<br>Criteria for Discontinuing Primary Prophylaxis<br>• N/A<br>Criteria for Restarting Primary Prophylaxis<br>• N/A | November 6, 2013 |
| Human Papillomavirus (HPV) | HPV vaccine | N/A | See Figures 1 and 2 for detailed vaccine recommendations. | November 6, 2013 |
| Isosporiasis (Cystoisosporiasis) | There are no U.S. recommendations for primary prophylaxis of isosporiasis. | N/A | Initiation of ART to avoid severe immunodeficiency may reduce incidence; TMP-SMX prophylaxis may reduce incidence. | February 8, 2019 |
| Malaria | For Travel to Chloroquine-Sensitive Areas—<br>• Chloroquine base 5 mg/kg body weight base by mouth, up to 300 mg once weekly (equivalent to 7.5 mg/kg body weight chloroquine phosphate). Start 1–2 weeks before leaving, take weekly while away, and then take once weekly for 4 weeks after returning home. | N/A | Recommendations are the same for HIV-infected and HIV-uninfected children. Please refer to the following website for the most recent recommendations based on region and drug susceptibility: https://www.cdc.gov/malaria/.<br>For travel to chloroquine-sensitive areas. Equally recommended options include chloroquine, atovaquone/proguanil, doxycycline (for children aged ≥8 years), and mefloquine; | November 6, 2013 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home<br>o 11–20 kg; one pediatric tablet (62.5 mg/25 mg)<br>o 21–30 kg, two pediatric tablets (125 mg/50 mg)<br>o 31–40 kg; three pediatric tablets (187.5 mg/75 mg)<br>o >40 kg; one adult tablet (250 mg/100 mg)<br>• Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1–2 days before travel, daily while away, and then up to 4 weeks after returning.<br>• Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg)<br>For Areas with Mainly *P. Vivax*—<br>• Primaquine phosphate 0.6 mg/kg body weight base once daily by mouth, up to a maximum of 30 mg base/day. Starting 1 day before leaving, taken daily, and for 3–7 days after return<br>For Travel to Chloroquine-Resistant Areas—<br>• Atovaquone/proguanil once daily started 1–2 days before travel, for | | primaquine is recommended for areas with mainly *P. vivax*.<br>G6PD screening must be performed prior to primaquine use.<br>Chloroquine phosphate is the only formulation of chloroquine available in the United States; 10 mg of chloroquine phosphate = 6 mg of chloroquine base.<br>For travel to chloroquine-resistant areas, preferred drugs are atovaquone/proguanil, doxycycline (for children aged ≥8 years), or mefloquine. | |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | duration of stay, and then for 1 week after returning home<br>o 11–20 kg; one pediatric tablet (62.5 mg/25 mg)<br>o 21–30 kg; two pediatric tablets (125 mg/50 mg)<br>o 31–40 kg; three pediatric tablets (187.5 mg/75 mg)<br>o >40 kg; one adult tablet (250 mg/100 mg)<br>• Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1–2 days before travel, daily while away, and then up to 4 weeks after returning.<br>• Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg) | | | |
| Microsporidiosis | N/A | N/A | Not recommended | December 14, 2016 |
| *Mycobacterium avium* Complex (MAC) | • Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, *or*<br>• Azithromycin 20 mg/kg body weight (maximum 1,200 mg) orally once weekly | • Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily<br>• Children aged >5 years: rifabutin 300 mg orally once daily with food | Primary Prophylaxis Indicated for Children<br>• Age <1 year: CD4 count <750 cells/$mm^3$<br>• Age 1 to <2 years: CD4 count <500 cells/$mm^3$<br>• Age 2 to <6 years: CD4 count <75 cells/$mm^3$<br>• Age ≥6 years: CD4 count <50 cells/$mm^3$<br>Criteria for Discontinuing Primary Prophylaxis | January 8, 2019 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | • **Do not discontinue** in children age <2 years.<br>• After ≥6 months of ART, *and:*<br>• Age 2 to <6 years: CD4 count >200 cells/mm$^3$ for >3 consecutive months<br>• Age ≥6 years: CD4 count >100 cells/mm$^3$ for >3 consecutive months<br>**Criteria for Restarting Primary Prophylaxis**<br>• Age 2 to <6 years: CD4 count <200 cells/mm$^3$<br>• Age ≥6 years: CD4 count <100 cells/mm$^3$ | |
| *Mycobacterium tuberculosis*<br>Treatment of LTBI, Also Known as TB Preventive Therapy | **Source Case Drug Susceptible**<br>• Age 2 to <12 years<br>o 12 weekly doses of isoniazid (25 mg/kg for children aged 2–12 years) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum)<br>• Age ≥12 years<br>o 12 doses of weekly isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum)<br>**Source Case Drug Resistant** | Rifampin 15–20 mg/kg (max 600 mg) daily for 4 months duration<br>*or*<br>isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 10–20 mg/kg (maximum 300 mg/day) for 3 months duration<br>*or*<br>isoniazid 10–15 mg/kg (max 300 mg) daily for 6–9 months | **Indications**<br>• Positive TST (TST ≥5 mm in children with HIV) or IGRA without previous TB treatment<br>• Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis)<br>**Considerations**<br>• TB disease must be excluded before starting treatment for latent TB infection.<br>• Drug–drug interactions with ART should be considered for all rifamycin-containing alternatives.<br>**Criteria for Discontinuing Prophylaxis**<br>• Only with documented severe adverse event, such as hepatotoxicity, hypersensitivity, or | September 14, 2023 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • For isoniazid-resistant source cases, daily rifampin 10–20 mg/kg (maximum 300 mg/day) for 4 months is recommended.<br>• For isoniazid- and rifampin-resistant (i.e., MDR-TB) source cases, consult a TB expert and local public health authorities. | | other adverse drug reactions, which are rare in children and adolescents.<br>Adjunctive Treatment<br>• Pyridoxine 1–2 mg/kg body weight once daily (maximum 25–50 mg/day) with isoniazid; pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all children with HIV; and pregnant adolescents and adults. | |
| *Pneumocystis jirovecii* Pneumonia | • TMP–SMX (Cotrimoxazole): Trimethoprim (2.5–5 mg/kg body weight/dose) with sulfamethoxazole (12.5–25 mg/kg body weight/dose twice per day). Dosing based on TMP component.<br>• The total daily dose should not exceed 320 mg trimethoprim and 1,600 mg sulfamethoxazole. Several dosing schemes have been used successfully:<br>o Given 3 days per week on consecutive days or on alternate days<br>o Given 2 days per week on consecutive days or on alternate days<br>o Given every day (total daily dose of TMP 5–10 mg/kg body weight given as a single dose each day) | Dapsone<br>*Children Aged ≥1 Months*<br>• 2 mg/kg body weight (maximum 100 mg) by mouth once daily or 4 mg/kg body weight (maximum 200 mg) by mouth once weekly<br>Atovaquone<br>*Children Aged 1–3 Months and >24 Months–12 Years*<br>• 30–40 mg/kg body weight/dose by mouth once daily with food<br>*Children Aged 4–24 Months*<br>• 45 mg/kg body weight/dose by mouth once daily with food | Primary Prophylaxis Indicated for—<br>• All HIV-infected or HIV-indeterminate infants from aged 4–6 weeks to 12 months regardless of CD4 cell count/percentage<br>• HIV-infected children aged 1 to <6 years with CD4 count <500 cells/mm$^3$ or CD4 percentage <15%; HIV-infected children aged 6–12 years with CD4 count <200 cells/mm$^3$ or CD4 percentage <15%<br>Criteria for Discontinuing Primary Prophylaxis<br>**Note:** Do not discontinue in HIV-infected children aged <1 year<br>*After ≥6 Months of cART*<br>• Aged 1 to <6 years: CD4 percentage ≥15% or CD4 count is ≥500 cells/mm$^3$ for >3 consecutive months, *or* | November 6, 2013 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | *Children Aged ≥13 Years*<br>• 1,500 mg (10 cc oral yellow suspension) per dose by mouth once daily<br>Aerosolized Pentamidine<br>*Children Aged ≥5 Years*<br>• 300 mg every month via Respirgard II™ nebulizer (manufactured by Marquest; Englewood, Colorado) | • Aged ≥6 years: CD4 percentage ≥15% or CD4 count is ≥200 cells/mm$^3$ for >3 consecutive months<br>Criteria for Restarting Primary Prophylaxis<br>• Aged 1 to <6 years with CD4 percentage <15% or CD4 count <500 cells/mm$^3$<br>• Aged ≥6 years with CD4 percentage <15% or CD4 count <200 cells/mm$^3$ | |
| Syphilis | N/A | N/A | Primary Prophylaxis Indicated for—<br>• N/A<br>Criteria for Discontinuing Primary Prophylaxis<br>• N/A<br>Criteria for Restarting Primary Prophylaxis<br>• N/A | November 6, 2013 |
| Toxoplasmosis | TMP-SMX, 150/750 mg/m$^2$ body surface area once daily by mouth | Children **Aged ≥1 Month**<br>• Dapsone 2 mg/kg body weight or 15 mg/m$^2$ body surface area (maximum 25 mg) by mouth once daily, ***plus***<br>• Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, ***plus*** | Primary Prophylaxis Indicated for—<br>*IgG Antibody to Toxoplasma and Severe Immunosuppression*<br>• HIV-infected children aged <6 years with CD4 percentage <15%; HIV-infected children aged ≥6 years with CD4 count <100 cells/mm$^3$.<br>Criteria for Discontinuing Primary Prophylaxis | November 6, 2013 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • Leucovorin 5 mg by mouth every 3 days<br><br>Children **Aged 1**–3 Months and >24 Months<br><br>• Atovaquone 30 mg/kg body weight by mouth once daily<br><br>Children Aged 4–24 Months<br><br>• Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface area (maximum 25 mg) by mouth once daily, *plus*<br><br>• Leucovorin 5 mg by mouth every 3 days<br><br>Acceptable Alternative Dosage Schedules for TMP-SMX<br><br>• TMP-SMX 150/750 mg/m² body surface area per dose once daily by mouth three times weekly on 3 consecutive days per week<br><br>• TMP-SMX 75/375 mg/m² body surface area per dose twice daily by mouth every day | **Note:** Do not discontinue in children aged <1 year<br><br>• After ≥6 months of cART, and<br><br>• Aged 1 to <6 years: CD4 percentage is ≥15% for >3 consecutive months<br><br>• Aged ≥6 years: CD4 count >200 cells/mm³ for >3 consecutive months<br><br>Criteria for Restarting Primary Prophylaxis<br><br>• Aged 1 to <6 years with CD4 percentage <15%<br><br>• Aged ≥6 years with CD4 count <100 to 200 cells/mm³ | |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • TMP-SMX 75/375 mg/$m^2$ body surface area per dose twice daily by mouth three times weekly on alternate days | | |
| Varicella-Zoster Virus (VZV)<br>Pre-exposure Prophylaxis | Varicella vaccine | N/A | See Figure 1 for detailed vaccine recommendations. | December 9, 2019 |
| Varicella-Zoster Virus (VZV)<br>Primary (Post-exposure) Prophylaxis | VariZIG 125 IU/10 kg body weight (maximum 625 IU) IM, administered ideally within 96 hours (potentially beneficial up to 10 days) after exposure | If VariZIG is not available, IVIG 400 mg/kg body weight, administered once should be considered. IVIG should ideally be administered within 96 hours of exposure.<br>When passive immunization is not possible, some experts recommend prophylaxis with acyclovir 20 mg/kg body weight/dose (maximum dose acyclovir 800 mg) by mouth, administered four times a day for 7 days, beginning 7–10 days after exposure. | Primary Post-exposure Prophylaxis Indicated for—<br>• Patients with substantial exposure to varicella or zoster who have no verified history of varicella or zoster, *or* who are seronegative for VZV on a sensitive specific antibody assay, *or* who lack evidence of vaccination.<br>• Many experts limit the recommendation for passive immunization to varicella- or zoster-exposed children with HIV considered severely immunocompromised (i.e., in CDC Immunologic Category 3), especially if severely symptomatic (i.e., CDC Clinical Category C[a]) and experiencing a high HIV RNA plasma viral load.<br>• Some experts start acyclovir at first appearance of rash in children with HIV, rather than providing acyclovir as prophylaxis. | December 9, 2019 |

**Table 1. Primary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | **Note:** VariZIG is commercially available in the United States from a broad network of specialty distributers.<br><br>[a] Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children aged <13 years. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR Morb Mortal Wkly Rep*. 1994;43:1-19. Available at https://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf. | |

**Key to Acronyms:** ART = antiretroviral therapy; BSA = body surface area; cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; CrCl = creatinine clearance; FDA = Food and Drug Administration; HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; HSV = herpes simplex virus; IgG = immunoglobulin G; IGRA = interferon-gamma release assay; IVIG = intravenous immunoglobulin; LTBI = latent TB infection; MDR-TB = multidrug-resistant TB; QID = four times a day; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; TST = tuberculin skin test; VZV = varicella-zoster virus

## Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

**Updated:** September 14, 2023
**Reviewed:** September 14, 2023

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Bacterial Infections<br>(*S. pneumoniae* and other invasive bacteria) | • TMP-SMX 75/375 mg/$m^2$ body surface area per dose by mouth twice daily | • IVIG 400 mg/kg body weight every 2–4 weeks | Secondary Prophylaxis Indicated<br>• >2 serious bacterial infections in a 1-year period in children who are unable to take cART<br>Criteria for Discontinuing Secondary Prophylaxis<br>• Sustained (≥ 3 months) immune reconstitution (CD4 percentage ≥25% if ≤6 years old; CD4 percentage ≥20% or CD4 count >350 cells/$mm^3$ if >6 years old)<br>Criteria for Restarting Secondary Prophylaxis<br>• >2 serious bacterial infections in a 1-year period despite cART | November 6, 2013 |
| Candidiasis | Not routinely recommended but can be considered for frequent severe recurrences.<br>Fluconazole<br>• Fluconazole 6–12 mg/kg body weight (maximum 600 mg/dose) by mouth three times weekly | Fluconazole<br>• Fluconazole 6–12 mg/kg body weight daily (maximum 200 mg) by mouth, or itraconazole oral solution, 2.5 mg/kg body weight/dose twice daily | Secondary Prophylaxis Indicated<br>• Frequent or severe recurrences<br>• Limited data in children<br>Criteria for Discontinuing Secondary Prophylaxis<br>• When CD4 count or percentage has risen to CDC immunologic Category 2 or 1 | January 31, 2019 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | Criteria for Restarting Secondary Prophylaxis<br>• Frequent severe recurrences | |
| Coccidioidomycosis | Fluconazole 6 mg/kg body weight (maximum 400 mg) by mouth once daily | Itraconazole 2–5 mg/kg body weight (maximum 200 mg) by mouth per dose twice daily | Lifelong secondary prophylaxis with fluconazole for patients with meningitis or disseminated disease in the immunocompromised patient is recommended. Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm$^3$ or CD4 percentage <15%. | November 6, 2013 |
| Cryptococcosis[a] | Fluconazole 6 mg/kg body weight (maximum 200 mg) by mouth once daily | Itraconazole oral solution 5 mg/kg body weight (maximum 200 mg) by mouth once daily | Secondary Prophylaxis Indicated<br>• Documented disease<br>Criteria for Discontinuing Secondary Prophylaxis<br>*If All of the Following Criteria Are Fulfilled:*<br>• Age ≥6 years<br>• Asymptomatic on ≥12 months of secondary prophylaxis<br>• CD4 count ≥100 cells/mm$^3$ with undetectable HIV viral load on cART for >3 months<br>Criteria for Restarting Secondary Prophylaxis<br>• CD4 count <100/mm$^3$<br>[a] Secondary prophylaxis is also referred to as maintenance therapy or suppressive therapy. | November 6, 2013 |
| Cryptosporidiosis | N/A | N/A | N/A | August 29, 2019 |

## Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Cytomegalovirus (CMV) | • Ganciclovir 5 mg/kg body weight IV once daily; *or*<br>• For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food; *or*<br>• For children aged 4 months to 16 years, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 x BSA x CrCl (up to maximum CrCl of 150 mL/min/1.73 $m^2$) orally once daily with food; *or*<br>• Foscarnet 90–120 mg/kg body weight IV once daily | • Cidofovir 5 mg/kg body weight per dose IV every other week. Must be given with probenecid and IV hydration. | **Secondary Prophylaxis Indicated for—**<br>• Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse.<br>**Criteria for Discontinuing Secondary Prophylaxis (All of the Following Criteria Must Be Fulfilled)**<br>• Completed ≥6 months of ART<br>• Age <6 years with CD4 percentage ≥15% for >6 consecutive months<br>• Age ≥6 years with CD4 count >100 cells/$mm^3$ for >6 consecutive months<br>• Consultation with ophthalmologist (if retinitis)<br>o Routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis.<br>**Criteria for Restarting Secondary Prophylaxis**<br>• Age <6 years with CD4 percentage <15%<br>• Age ≥6 years with CD4 count <100 cells/$mm^3$ | August 3, 2023 |
| Giardiasis | N/A | N/A | N/A | August 22, 2019 |
| Hepatitis B Virus (HBV) | Hepatitis A Vaccine | N/A | **Secondary Prophylaxis Indicated for—**<br>• Chronically HBV-infected individuals to prevent further liver injury.<br>**Criteria for Discontinuing Secondary Prophylaxis**<br>• N/A | November 6, 2013 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | Criteria for Restarting Secondary Prophylaxis<br>• N/A | |
| Hepatitis C Virus (HCV) | None | N/A | N/A | November 6, 2013 |
| Herpes Simplex Virus (HSV) Infections | Mucocutaneous Disease<br>• Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth BID<br>Suppressive Therapy After Neonatal HSV Disease (Skin, Eye, Mouth, CNS, or Disseminated Disease)<br>• Acyclovir 300 mg/$m^2$ body surface area/dose by mouth TID for 6 months | Mucocutaneous Disease, for Adolescents Old Enough to Receive Adult Dosing<br>• Valacyclovir 500 mg by mouth BID, or<br>• Famciclovir 500 mg by mouth BID | Secondary Prophylaxis Indicated<br>• Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease.<br>Criteria for Discontinuing Secondary Prophylaxis<br>• After a prolonged period (e.g., 1 year) of prophylaxis, consider suspending prophylaxis and determine with the patient whether additional prophylaxis is necessary. Although level of immune reconstitution is a consideration, no specific CD4 threshold has been established. | June 27, 2018 |
| Histoplasmosis (Suppressive Therapy) | Itraconazole oral solution 5–10 mg/kg body weight (maximum 200 mg) per dose by mouth daily | Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily | Secondary Prophylaxis Indicated<br>• Documented histoplasmosis in a patient with impaired immune function<br>Criteria For Discontinuing Secondary Prophylaxis<br>*If All of the Following Criteria Are Fulfilled:*<br>• CD4 percentage >15% at any age; or CD4 cell count >150 cells/$mm^3$ aged ≥6 years.<br>• Received ≥1 year itraconazole maintenance therapy | November 6, 2013 |

## Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | • Established (e.g., ≥6 months) adherence to effective cART<br>• Negative *Histoplasma* blood cultures<br>• Serum Histoplasma antigen <2 ng/mL<br><br>Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules. | |
| Human Papillomavirus (HPV) | N/A | N/A | N/A | November 6, 2013 |
| Isosporiasis (Cystoisosporiasis) | If Severe Immunosuppression—<br>• TMP-SMX 2.5 mg/kg body weight of the TMP component (maximum 80 mg TMP) twice daily by mouth three times per week | Pyrimethamine 1 mg/kg body weight (maximum 25 mg) *plus* folinic acid, 5–15 mg by mouth once daily.<br><br>Second-Line Alternative<br>• Ciprofloxacin, 10–20 mg/kg body weight (maximum 500 mg) by mouth three times per week | Consider discontinuing secondary prophylaxis in patients without evidence of active *Isospora* infection who have sustained improvement in immunologic status (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for >6 months in response to ART.<br><br>In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no data exist for dosing in children. Thus, the recommended dose for secondary prophylaxis in children is pyrimethamine 1 mg/kg (maximum 25 mg) by mouth once daily.<br><br>Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues. | February 8, 2019 |
| Malaria | For *P. vivax* or *P. ovale:* | N/A | This regimen, known as PART, is recommended only for individuals who have resided in a | November 6, 2013 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Primaquine 0.5 mg/kg base (0.8mg/kg salt) up to adult dose orally, daily for 14 days after departure from the malarious area | | malaria-endemic area for an extended period of time. Adult dose: 30 mg base (52.6 mg salt) orally, daily for 14 days after departure from the malarious area.<br><br>http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#1939 | |
| Microsporidiosis | Disseminated, Non-ocular Infection or GI Infection Caused by Microsporidia Other Than *E. bieneusi* or *V. corneae*<br><br>• Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily<br><br>Ocular Infection<br><br>• Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) *plus*, for infection attributed to microsporidia other than *E. bieneusi* or *V. corneae*, *albendazole* 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection | N/A | Criteria for Discontinuing Secondary Prophylaxis<br><br>• After initiation of ART, resolution of signs and symptoms and sustained immune reconstitution (more than 6 months at CDC immunologic category 1 or 2) | December 15, 2016 |
| *Mycobacterium avium* Complex (MAC)<br>(Chronic Suppressive Therapy) | • Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, *plus* | • Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily, *plus*<br><br>• Ethambutol 15–25 mg/kg body weight (maximum | Secondary Prophylaxis Indicated<br><br>• Prior disease | January 8, 2019 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food<br>• Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food | 2.5 g) orally once daily, with or without food<br>• Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food | Criteria for Discontinuing Secondary Prophylaxis<br>*Fulfillment of All of the Following Criteria:*<br>• Completed ≥6 months of ART<br>• Completed ≥12 months MAC therapy<br>• Asymptomatic for signs and symptoms of MAC<br>• Aged 2 to <6 years: CD4 count >200 cells/mm$^3$ for ≥6 consecutive months<br>• Aged ≥6 years: CD4 count >100 cells/mm$^3$ for ≥6 consecutive months<br>Criteria for Restarting Secondary Prophylaxis<br>• Aged 2 to <6 years: CD4 count <200 cells/mm$^3$<br>• Aged ≥6 years: CD4 count <100 cells/mm$^3$ | |
| *Mycobacterium tuberculosis* | N/A | N/A | N/A | September 14, 2023 |
| *Pneumocystis* Pneumonia | • TMP-SMX (Cotrimoxazole): TMP 2.5–5 mg/kg body weight/dose with SMX 12.5–25 mg/kg body weight/dose twice per day. Dosing based on TMP component.<br>• The total daily dose should not exceed 320 mg TMP and 1,600 mg SMX. Several dosing schemes have been used successfully— | Dapsone<br>*Children Aged ≥1 Months*<br>• 2 mg/kg body weight (maximum 100 mg) by mouth once daily or 4 mg/kg body weight (maximum 200 mg) by mouth once weekly | Secondary Prophylaxis Indicated for—<br>• Children with prior episode of PCP<br>Criteria for Discontinuing Secondary Prophylaxis<br>• Same as for primary prophylaxis<br>Criteria for Restarting Secondary Prophylaxis<br>• Same as for primary prophylaxis | November 6, 2013 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | o Given 3 days per week on consecutive days or on alternate days<br>o Given 2 days per week on consecutive days or on alternate days<br>o Given every day (total daily dose of TMP 5–10 mg/kg body weight given as a single dose each day) | Atovaquone<br>*Children Aged 1–3 Months and >24 Months–12 Years*<br>• 30-40 mg/kg body weight/dose by mouth once daily with food<br>*Children Aged 4–24 Months*<br>• 45 mg/kg body weight/dose by mouth once daily with food<br>*Children Aged ≥13 Years*<br>• 1,500 mg (10 cc oral yellow suspension) per dose by mouth once daily<br>Aerosolized Pentamidine<br>*Children Aged ≥5 Years*<br>• 300 mg every month via Respirgard II™ nebulizer (manufactured by Marquest; Englewood, Colorado) | | |
| Syphilis | N/A | N/A | Secondary Prophylaxis Indicated<br>• N/A<br>Criteria for Discontinuing Secondary Prophylaxis<br>• N/A | November 6, 2013 |

**Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | Criteria for Restarting Secondary Prophylaxis<br>• N/A | |
| Toxoplasmosis<br>(Suppressive Therapy) | • Sulfadiazine 42.5–60 mg/kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, ***plus***<br>• Pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface area (maximum 25 mg) by mouth once daily, ***plus***<br>• Leucovorin 5 mg by mouth once every 3 days | • Clindamycin 7–10 mg/kg body weight per dose by mouth three times daily, ***plus***<br>• Pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface area (maximum 25 mg) by mouth once daily, ***plus***<br>• Leucovorin 5 mg by mouth once every 3 days<br>*Children Aged 1–3 Months and >24 Months*<br>• Atovaquone 30 mg/kg body weight by mouth once daily<br>• Leucovorin, 5 mg by mouth every 3 days<br>• TMP-SMX, 150/750 mg/m² body surface area once daily by mouth<br>*Children Aged 4–24 Months*<br>• Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface | Secondary Prophylaxis Indicated<br>• Prior toxoplasmic encephalitis<br>Note: Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens<br>Criteria for Discontinuing Secondary Prophylaxis<br>*If All of the Following Criteria are Fulfilled:*<br>• Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, *and*<br>• Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months<br>• Aged ≥6 years; CD4 cell count >200 cells/mm³ for >6 consecutive months<br>Criteria for Restarting Secondary Prophylaxis<br>• Aged 1 to <6 years with CD4 percentage <15%<br>• Aged ≥6 years with CD4 cell count <200 cells/mm³ | November 6, 2013 |

## Table 2. Secondary Prophylaxis of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
| --- | --- | --- | --- | --- |
| | | area (maximum 25 mg) by mouth once daily, *plus*<br>• Leucovorin, 5 mg by mouth every 3 days<br>• TMP-SMX, 150/750 mg/m$^2$ body surface area once daily by mouth | | |
| Varicella-Zoster Virus (VZV) | N/A | N/A | There is no indication for secondary prophylaxis. | December 9, 2019 |

Key to Acronyms: BID = twice daily; BSA = body surface area; cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers of Disease Control and Prevention; CNS = central nervous system; CrCl = (estimated) creatinine clearance, CSF = cerebrospinal fluid; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; IV = intravenous; IVIG = intravenous immunoglobulin; MAC = mycobacterium avium complex; PCP = pneumocystis pneumonia; QID = four times a day; SQ = subcutaneous; TE = toxoplasmic encephalitis; TID = three times daily; TMP-SMX = trimethoprim-sulfamethoxazole

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

Updated: September 14, 2023
Reviewed: September 14, 2023

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Bacterial Infections<br><br>Bacterial pneumonia; *S. pneumoniae;* occasionally *S. aureus, H. influenzae, P. aeruginosa* | • Ceftriaxone 50–100 mg/kg body weight per dose once daily, or 25–50 mg/kg body weight per dose twice daily IV or IM (max 4 g/day), *or*<br>• Cefotaxime 40–50 mg/kg body weight per dose 4 times daily, or 50–65 mg/kg body weight 3 times daily (max 8–10 g/day) IV | • Cefuroxime, 35–50 mg/kg body weight per dose 3 times daily (max 4–6 g/day) IV | For children who are receiving effective cART, have mild or no immunosuppression, and have mild to moderate community-acquired pneumonia, oral therapy option would be amoxicillin 45 mg/kg body weight per dose twice daily (maximum dose: 4 g per day).<br><br>Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (*M. pneumoniae, C. pneumoniae*).<br><br>Add clindamycin or vancomycin if methicillin-resistant *S. aureus* is suspected (base the choice on local susceptibility patterns).<br><br>For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (such as ceftazidime or cefepime instead of ceftriaxone).<br><br>Consider PCP in patients with severe pneumonia or more advanced HIV disease. | November 6, 2013 |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | Evaluate for tuberculosis, cryptococcosis, and endemic fungi as epidemiology suggests. | |
| Candidiasis | Oropharyngeal<br>• Fluconazole 6–12 mg/kg body weight (maximum 400 mg/dose) by mouth once daily<br>• Clotrimazole troches, 10-mg troche by mouth 4–5 times daily<br>• Nystatin suspension 4–6 mL by mouth 4 times daily, *or* 1–2, 200,000-unit flavored pastilles by mouth 4–5 times daily<br>*Treatment Duration*<br>• 7 to 14 days | Oropharyngeal (Fluconazole-Refractory)<br>• Itraconazole oral solution 2.5 mg/kg body weight/dose by mouth twice daily (maximum 200–400 mg/day) | Itraconazole oral solution **should not** be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease.<br>Central venous catheters should be removed, when feasible, in children with HIV with fungemia.<br>In uncomplicated catheter-associated *C. albicans* candidemia, an initial course of amphotericin B followed by fluconazole to complete treatment can be used (use invasive disease dosing).<br>Voriconazole has been used to treat esophageal candidiasis in a small number of immunocompromised children without HIV.<br>Voriconazole Dosing in Pediatric Patients<br>• Voriconazole 9 mg/kg body weight/dose every 12 hours IV loading for day 1, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. | January 31, 2019 |
| | Esophageal Disease<br>• Fluconazole 6–12 mg/kg body weight by mouth once daily (maximum dose: 600 mg)<br>• Itraconazole oral solution, 2.5 mg/kg body weight/dose by mouth twice daily<br>*Treatment Duration*<br>• Minimum of 3 weeks and for at least 2 weeks following the resolution of symptoms | Esophageal Disease<br>• Amphotericin B (deoxycholate) 0.3–0.7 g/kg body weight IV once daily<br>Echinocandins<br>*Anidulafungin*<br>• *Aged 2–17 years*: Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV<br>• *Aged ≥18 years*: 200-mg loading dose, then 100 mg/dose daily IV | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | *Caspofungin*<br>• *Infants aged <3 months*: 25 mg/m² BSA/dose daily IV<br>• *Aged 3 months–17 years*: 70 mg/m²/day IV loading dose followed by 50 mg/m²/day IV (maximum 70 mg). Note: Dosing of caspofungin for children should be based on body surface area.<br>• *Aged ≥18 years*: 70-mg loading dose IV, then 50 mg/dose daily IV<br>*Micafungin*<br>• Note: In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below).<br>• *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations.<br>• *Infants <15 kg body weight*: 5–7 mg/kg body weight/dose daily IV<br>• *Children ≤40 kg body weight and aged 2–8 years*: 3–4 mg/kg body weight/dose daily IV<br>• *Children ≤40 kg body weight and aged 9–17 years*: 2–3 mg/kg body weight/dose daily IV<br>• *Children >40 kg body weight*: 100 mg/dose daily IV | • Conversion to oral voriconazole should be at 9 mg/kg body weight/dose orally every 12 hours.<br>• Children aged ≥12 years and weighing at least 40 kg can use adult dosing (load voriconazole 6 mg/kg body weight/dose every 12 hours IV on day 1, followed by 4 mg/kg body weight/dose every 12 hours IV. Conversion to oral therapy at 200 mg every 12 hours by mouth).<br>Anidulafungin in Children Aged 2–17 Years<br>• Loading dose of 3 mg/kg body weight/once daily followed by 1.5 mg/kg body weight/once daily (100 mg/day maximum).<br>Fluconazole Dosing Considerations<br>• If a neonate’s creatinine level is >1.2 mg/dL for >3 consecutive doses, the dosing interval for fluconazole 12 mg/kg body weight may be prolonged to one dose every 48 hours until the serum creatinine level is <1.2 mg/dL<br>• *Aged ≥18 Years*: 400 mg/dose once daily (6 mg/kg body weight once daily). | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | *IV Fluconazole*<br>• *Children*: 6–12 mg/kg body weight/dose daily for infants and children of all ages (maximum dose: 600 mg daily). | | |
| | Invasive Disease<br>*Critically Ill*<br>• Echinocandin Recommended<br>• Anidulafungin<br>o *Aged 2–17 years*: Load with 3 mg/kg body weight/daily dose and then maintenance dose at 1.5 mg/kg body weight once daily<br>o *Aged ≥18 years*: 200 mg loading dose, then 100 mg once daily<br>• Caspofungin<br>o *Infants aged <3 months*: 25 mg/m² BSA/dose once daily IV<br>o *Aged 3 months–17 years:* 70 mg/m² BSA/day loading dose followed by 50 mg/m² once daily (maximum 70 mg) **Note:** Dosing of caspofungin in children should be based on body surface area. | Invasive Disease<br>• Fluconazole 12 mg/kg body weight IV once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia)<br>• Lipid formulations of amphotericin B, 5 mg/kg body weight IV once daily<br>• Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | o *Aged ≥18 years*: 70-mg loading dose, then 50 mg once daily<br>• Micafungin<br>o **Note:** In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below).<br>o *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations.<br>o Infants <15 kg body weight: 5–7 mg/kg/day<br>o Children ≤40 kg body weight and aged 2–8 years: 3–4 mg/kg body weight/dose daily IV<br>o Children ≤40 kg body weight and aged 9–17 years: 2–3 mg/kg body weight/dose daily<br>o Children >40 kg body weight: 100 mg/dose daily IV | | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Treatment Duration<br>o Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture.<br>*Not Critically Ill*<br>• Fluconazole Recommended<br>o 12 mg/kg body weight/dose daily IV (maximum dose: 600 mg) for infants and children of all ages<br>o Avoid fluconazole for *C. krusei* and *C. glabrata*, avoid echinocandin for *C. parapsilosis*.<br>• Treatment Duration<br>o Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture. | | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Coccidioidomycosis | Severe Illness with Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease<br>• Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily, until clinical improvement.<br>• A lipid amphotericin B preparation can be substituted at a dose of 5 mg/kg body weight IV once daily (dosage of the lipid preparation can be increased to as much as 10 mg/kg body weight IV once daily for life-threatening infection).<br>• After the patient is stabilized, therapy with an azole (fluconazole or itraconazole) can be substituted and continued to complete a 1-year course of antifungal therapy. | Severe Illness with Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease (If Unable to Use Amphotericin)<br>• Fluconazole 12 mg/kg body weight (maximum 800 mg) per dose IV or by mouth once daily<br>• Treatment is continued for total of 1 year, followed by secondary prophylaxis. | Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful.<br>Itraconazole is the preferred azole for treatment of bone infections.<br>Some experts initiate an azole during amphotericin B therapy; others defer initiation of the azole until after amphotericin B is stopped.<br>For treatment failure, can consider voriconazole, caspofungin, or posaconazole (or combinations). However, experience is limited, and definitive pediatric dosages have not been determined.<br>Options should be discussed with an expert in the treatment of coccidioidomycosis.<br>Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease and is continued lifelong for meningeal disease. | November 6, 2013 |
| | Meningeal Infection<br>• Fluconazole 12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily followed by secondary lifelong prophylaxis. | Meningeal Infection (Unresponsive to Fluconazole)<br>• IV amphotericin B plus intrathecal amphotericin B followed by secondary prophylaxis. **Note:** Expert consultation recommended. | | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia)<br>• Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily. | Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia)<br>• Itraconazole 2–5 mg/kg body weight per dose (maximum dose 200 mg) per dose IV or by mouth 3 times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) by mouth per dose twice daily thereafter.<br>• Duration of treatment determined by rate of clinical response. | Therapy with amphotericin results In a more rapid clinical response in severe, non-meningeal disease. | |
| Cryptococcosis | CNS Disease<br>*Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)*<br>• Amphotericin B deoxycholate 1.0 mg/kg body weight (or liposomal amphotericin B 6 mg/kg body weight) IV once daily **plus** flucytosine 25 mg/kg body weight per dose by mouth given 4 times daily<br>*Consolidation Therapy (Followed by Secondary Prophylaxis)*<br>• Fluconazole 12 mg/kg body weight on day 1, then 10–12 mg/kg body weight (max 800 mg) once daily IV or by mouth for a minimum of 8 weeks | CNS Disease<br>*Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)*<br>• If Flucytosine Not Tolerated or Unavailable—<br>o **A.** Liposomal amphotericin B, 6 mg/kg body weight IV once daily, **or** Amphotericin B Lipid Complex, 5 mg/kg body weight IV once daily, **or** Amphotericin B deoxycholate, 1.0–1.5 mg/kg body weight IV once daily **alone or B. in combination** with high-dose fluconazole (12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight [max 800 mg] IV). **Note:** Data-driven pediatric dosing guidelines are unavailable for fluconazole with use of such combination therapy. | In patients with meningitis, CSF culture should be negative prior to initiating consolidation therapy.<br>Overall, *in vitro* resistance to antifungal agents used to treat cryptococcosis remains uncommon. Newer azoles (voriconazole, posaconazole, ravuconazole) are all very active *in vitro* against *C. neoformans* but published clinical experience on their use for cryptococcosis is limited.<br>Liposomal amphotericin and amphotericin B lipid complex are especially useful for children with renal insufficiency or infusion-related toxicity to amphotericin B deoxycholate. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • If Amphotericin B-Based Therapy Not Tolerated—<br>o Fluconazole, 12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily **plus** flucytosine, 25 mg/kg body weight per dose by mouth given 4 times daily<br>• Consolidation Therapy (Followed by Secondary Prophylaxis)<br>o Itraconazole 5–10 mg/kg body weight by mouth given once daily, or 2.5–5 mg/kg body weight given twice daily (maximum 200 mg/dose) for a minimum of 8 weeks. A loading dose (2.5–5 mg/kg body weight per dose 3 times daily) is given for the first 3 days (maximum 200 mg/dose; 600 mg/day). See comment on itraconazole under Other Options/Issues. | Liposomal amphotericin and amphotericin B lipid complex are **significantly** more expensive than amphotericin B deoxycholate.<br><br>Liquid preparation of itraconazole (if tolerated) is preferable to tablet formulation because of better bioavailability, but it is more expensive. Bioavailability of the solution is better than the capsule, but there were no upfront differences in dosing range based on preparation used. Ultimate dosing adjustments should be guided by itraconazole levels.<br><br>Serum itraconazole concentrations should be monitored to optimize drug dosing.<br><br>Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake, or impair its renal excretion, or both.<br><br>Flucytosine dose should be adjusted to keep 2-hour post-dose drug levels at 40–60 µg/mL.<br><br>Oral acetazolamide should not be used for reduction of ICP in cryptococcal meningitis. | |
| | Localized Disease, Including Isolated Pulmonary Disease (CNS Not Involved)[a]<br>• Fluconazole 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily | Localized Disease Including Isolated Pulmonary Disease (CNS Not Involved)[a]<br>• Amphotericin B, 0.7–1.0 mg/kg body weight, *or*<br>• Amphotericin liposomal 3–5 mg/kg body weight, *or*<br>• Amphotericin lipid complex, 5 mg/kg body weight IV once daily | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[a]<br>• Amphotericin B 0.7–1.0 mg/kg body weight, *or*<br>• Liposomal amphotericin, 3–5 mg/kg body weight, *or*<br>• Amphotericin B lipid complex 5 mg/kg body weight IV once daily (± flucytosine) | Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[a]<br>• Fluconazole, 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily | Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis.<br><br>Secondary prophylaxis is recommended following completion of initial therapy (induction plus consolidation)—drugs and dosing listed above.<br><br>[a] Duration of therapy for non-CNS disease depends on site and severity of infection and clinical response | |
| Cryptosporidiosis | Effective ART<br>• Immune reconstitution might lead to parasitologic and clinical response | There is no consistently effective therapy for cryptosporidiosis in patients with HIV infection; optimized ART and a trial of nitazoxanide should be considered.<br><br>Nitazoxanide<br>• 1–3 years of age: Nitazoxanide (20 mg/mL oral solution) 100 mg orally twice daily with food<br>• 4–11 years of age: Nitazoxanide (20 mg/mL oral solution) 200 mg orally twice daily with food<br>• ≥12 years of age: Nitazoxanide tablet 500 mg orally twice daily with food<br><br>*Treatment Duration*<br>• 3–14 days | Supportive Care<br>• Hydration, correct electrolyte abnormalities, nutritional support<br><br>Antimotility agents (such as loperamide) should be used with caution in young children. | August 29, 2019 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Cytomegalovirus (CMV) | Symptomatic Congenital Infection with Neurologic Involvement<br>• Ganciclovir 6 mg/kg body weight per dose IV every 12 hours for 6 weeks, *or*<br>• Valganciclovir 16 mg/kg body weight per dose orally twice daily for 6 months | | Data on valganciclovir dosing in young children for treatment of retinitis are unavailable, but consideration can be given to transitioning from IV ganciclovir to oral valganciclovir after improvement of retinitis is noted.<br><br>Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children.<br><br>Combination ganciclovir and foscarnet is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children is unknown, particularly if receiving optimized ART.<br><br>Chronic suppressive therapy (secondary prophylaxis) is recommended in adults and children following initial therapy of disseminated disease, retinitis, neurologic disease, or GI disease with relapse. | August 3, 2023 |
| | Disseminated Disease and Retinitis<br>*Induction Therapy*<br>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours for 14–21 days (may be increased to 7.5 mg/kg body weight per dose IV twice daily)<br>*Chronic Maintenance Therapy*<br>• Ganciclovir 5 mg/kg body weight once daily for 5–7 days | Disseminated Disease and Retinitis<br>*Induction Therapy*<br>• Foscarnet, 60 mg/kg body weight per dose IV every 8 hours or 90 mg/kg body weight per dose IV every 12 hours for 14–21 days<br>*Chronic Maintenance Therapy*<br>• Foscarnet 90–120 mg/kg body weight IV once daily<br>*Alternative Therapy for Retinitis (Followed by Chronic Maintenance Therapy; See Cytomegalovirus Row in Secondary Prophylaxis Table)*<br>• Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above).<br>  o **Note:** This is an option in older children who can receive the adult dose (based on their BSA) and in patients with mild disease. | | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • IV ganciclovir **plus** IV foscarnet (at above induction doses) may be considered as initial induction therapy in children with sight-threatening disease or for treatment following failure/relapse on monotherapy.<br>• Cidofovir is also used to treat CMV retinitis in adults who are intolerant to other therapies. Induction dosing in adults is 5 mg/kg body weight IV once weekly for 2 weeks, followed by chronic suppressive therapy (see Cytomegalovirus row in Secondary Prophylaxis table); however, data on dosing in children are unavailable. Must be given with probenecid and IV hydration. | | |
| | Central Nervous System Disease<br>*Induction Therapy*<br>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours **plus** foscarnet 60 mg/kg body weight per dose IV every 8 hours (or 90 mg/kg body weight per dose IV every 12 hours) continued until symptomatic improvement<br>*Chronic Maintenance Therapy*<br>• See Cytomegalovirus row in Secondary Prophylaxis table. | | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Giardiasis | • Tinidazole, 50 mg/kg by mouth, administered as 1 dose given with food (maximum 2 g). **Note:** Based on data from children who are HIV-negative<br>• Nitazoxanide<br>  o *1–3 years*: 100 mg by mouth every 12 hours with food for 3 days<br>• *4–11 years*: 200 mg by mouth every 12 hours with food for 3 days<br>• ≥*12 years*: 500 mg by mouth every 12 hours with food for 3 days<br>**Note:** Based on data from children who are HIV-negative | Metronidazole 5 mg/kg by mouth every 8 hours for 5–7 days.<br>**Note:** Based on data from children who are HIV-negative | Tinidazole is FDA-approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed.<br>Metronidazole has a high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA-approved for the treatment of giardiasis.<br>**Supportive Care**<br>• Hydration<br>• Correction of electrolyte abnormalities<br>• Nutritional support<br>Antimotility agents (e.g., loperamide) should be used with caution in young children. | August 22, 2019 |
| Hepatitis B Virus (HBV) | **Treatment of Only HBV Required (Child Does Not Require cART)**<br>• IFN-α 3 million units/m² body surface area SQ 3 times a week for 1 week, followed by dose escalation to 6 million units/m² body surface area (max 10 million units/dose), to complete a 24-week course, *or* | • IFN-α 10 million units/m² body surface area SQ 3 times a week for 6 months (sometimes used for retreatment of failed lower-dose interferon therapy)<br>• Alternative for 3TC: FTC 6 mg/kg body weight (maximum 200 mg) once daily | **Indications for Treatment Include:**<br>• Detectable serum HBV DNA, irrespective of HBeAg status, for >6 months; and<br>• Persistent (>6 months) elevation of serum transaminases (≥ twice the upper limit of normal); or<br>• Evidence of chronic hepatitis on liver biopsy | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • For children aged ≥12 years, adefovir 10 mg by mouth once daily for a minimum of 12 months (uncertain if risk of HIV resistance)<br><br>Treatment of Both HIV And HBV Required (Child Not Already Receiving 3TC or FTC)<br><br>• 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive cART regimen<br><br>• For children aged ≥2 years, include TDF as part of cART regimen with 3TC or FTC. For children aged ≥12, TDF dose is 300 mg once daily. For children aged <12 year, and 8 mg/kg body weight per dose once daily (maximum dose 300 mg)<br><br>Treatment of Both HIV and HBV Required (Child Already Receiving cART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance)<br><br>• For children aged ≥2 years, include TDF as part of cART regimen with 3TC or FTC. For children aged ≥12 years, TDF dose is 300 mg once daily. For children aged <12 years, 8 mg/kg body weight per dose once daily (maximum dose 300 mg) | | IFN-α is contraindicated in children with decompensated liver disease; significant cytopenias, severe renal, neuropsychiatric, or cardiac disorders; and autoimmune disease.<br><br>Choice of HBV treatment options for HIV/HBV-co-infected children depends upon whether concurrent HIV treatment is warranted.<br><br>3TC and FTC have similar activity (and have cross-resistance) and should not be given together. FTC is not FDA-approved for treatment of HBV.<br><br>TDF is approved for use in treatment of HIV infection in children aged ≥2 years but it is not approved for treatment of HBV infection in children aged <12 years. It should only be used for HBV in HIV/HBV-infected children as part of a cART regimen.<br><br>Adefovir is approved for use in children aged ≥12 years.<br><br>ETV is not approved for use in children younger than age 16 years, but is under study in HIV-uninfected children for treatment of chronic hepatitis B. Can be considered for older HIV-infected children who can receive adult dosage. It should only be used for HBV in HIV/HBV-infected children who also receive an HIV-suppressive cART regimen. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • For children aged ≥12 years, add adefovir 10 mg by mouth once daily or entecavir 0.5 mg by mouth once daily in addition to cART regimen.<br>• For children aged <12 years, give 6-month course of IFN-α as above in addition to cART regimen. | | IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6 to 12 weeks of cART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS.<br><br>In children receiving TDF and 3TC or FTC, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HIV/HBV therapy has begun, it should be continued unless contraindicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation.<br><br>If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening.<br><br>Telbivudine has been approved for use in people aged ≥16 years with HBV; there are no data on safety or efficacy in children aged <16 years; a pharmacokinetic study is under way in HIV-uninfected children. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Hepatitis C Virus (HCV) | IFN-α **Plus Ribavirin Combination** Therapy<br><br>• Pegylated IFN-α: Peg-IFN 2a 180 µg/1.73 $m^2$ body surface area subcutaneously once per week (maximum dose 180 µg) OR Peg-IFN 2b 60 µg/$m^2$ body surface area once per week<br><br>PLUS<br><br>• Ribavirin (oral) 7.5 mg/kg body weight twice daily (fixed dose by weight recommended):<br>o 25–36 kg: 200 mg a.m. and p.m.<br>o >36 to 49 kg: 200 mg a.m. and 400 mg p.m.<br>o >49 to 61 kg: 400 mg a.m. and p.m.<br>o >61 to 75 kg: 400 mg a.m. and 600 mg p.m.<br>o >75 kg: 600 mg a.m. and p.m.<br><br>*Treatment Duration*<br><br>• 48 weeks, regardless of HCV genotype | None | Optimal duration of treatment for HIV/HCV-coinfected children is unknown and based on recommendations for HIV/HCV-coinfected adults<br><br>Treatment of HCV in children <3 years generally is not recommended.<br><br>Indications for treatment are based on recommendations in HIV/HCV-coinfected adults; because HCV therapy is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-coinfected children aged >3 years in whom there are no contraindications to treatment<br><br>For recommendations related to use of telaprevir or boceprevir in adults, including warnings about drug interactions between HCV protease inhibitors and HIV protease inhibitors and other antiretroviral drugs, see Adult OI guidelines.<br><br>IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6–12 weeks of cART. It may be difficult to distinguish between IRIS and drug-induced hepatotoxicity or other causes of hepatitis. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | IFN-α is contraindicated in children with decompensated liver disease, significant cytopenias, renal failure, severe cardiac disorders and non-HCV-related autoimmune disease.<br><br>Ribavirin is contraindicated in children with unstable cardiopulmonary disease, severe pre-existing anemia or hemoglobinopathy.<br><br>Didanosine combined with ribavirin may lead to increased mitochondrial toxicities; concomitant use is contraindicated.<br><br>Ribavirin and zidovudine both are associated with anemia, and when possible, should not be administered together. | |
| Herpes Simplex Virus Infections (HSV) | Neonatal CNS or Disseminated Disease<br>• Acyclovir 20 mg/kg body weight IV/dose every 8 hours for ≥21 days<br><br>Neonatal Skin, Eye, or Mouth Disease<br>• Acyclovir 20 mg/kg body weight IV/dose every 8 hours for 14 days | | For Neonatal CNS Disease—<br>• Repeat CSF HSV DNA PCR should be performed on days 19 to 21 of therapy. If the repeat CSF HSV DNA PCR is positive, continue IV acyclovir for an additional week, repeating the CSF HSV DNA PCR again near the end of extended treatment. Acyclovir should not be stopped until a repeat CSF HSV DNA PCR is negative. | June 27, 2018 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | CNS or Disseminated Disease in Children Outside the Neonatal Period<br>• Acyclovir 10 mg/kg body weight (up to 15 mg/kg body weight/dose in children <12 years) IV every 8 hours for 21 days | | | |
| | Moderate to Severe Symptomatic Gingivostomatitis<br>• Acyclovir 5–10 mg/kg body weight/dose IV every 8 hours. Patients can be switched to oral therapy after lesions have begun to regress and therapy continued until lesions have completely healed.<br>Mild Symptomatic Gingivostomatitis<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 7–10 days<br>Recurrent Herpes Labialis<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 5 days<br>For First-Episode Genital Herpes (Adults and Adolescents)—<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 7–10 days | • Valacyclovir is approved for immunocompetent adults and adolescents with first-episode mucocutaneous HSV at a dose of 1 g/dose by mouth BID for 7–10 days; also approved for recurrent herpes labialis in children ≥12 years using two, 2 g doses by mouth separated by 12 hours as single-day therapy.<br>• Recurrent genital HSV can be treated with valacyclovir 500 mg BID for 3 days or 1 g by mouth daily for 5 days.<br>• Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth BID for 1 day.<br>• Famciclovir is approved to treat primary genital HSV in immunocompetent adults at a dose of 250 mg/dose by mouth TID for 7–10 days.<br>• Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth BID at a 12-hour interval for 2 doses | • There is no pediatric preparation of valacyclovir (although crushed capsules can be used to make a suspension according to specific instructions provided in the U.S. FDA package insert) and data on dosing in children are limited. Valacyclovir can be used by adolescents able to receive adult dosing.<br>• Famciclovir is available in a sprinkle formulation with weight-adjusted dosing. Famciclovir can be used by adolescents able to receive adult dosing. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • Famciclovir is approved for use in HIV-infected adults and adolescents with recurrent mucocutaneous HSV infection at a dose of 500 mg/dose by mouth BID for 7 days. | | |
| | Recurrent Genital Herpes (Adults and Adolescents)<br>• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 5 days<br><br>Children with HSV Keratoconjunctivitis<br>• Often treated with topical trifluridine (1%) or granciclovir (0.15%) applied as 1–2 drops 5 times daily. Many experts add oral acyclovir to the topical therapy.<br><br>Children with ARN<br>• For children old enough to receive adult dose, acyclovir 10–15 mg/kg body weight/dose IV every 8 hours for 10–14 days, followed by oral valacyclovir 1 g/dose TID for 4–6 weeks<br>• As an alternative, oral acyclovir 20 mg/kg body weight/dose QID for 4–6 weeks after IV acyclovir for 10–14 days | | Alternative and Short-Course Therapy in Immunocompromised Adults with Recurrent Genital Herpes<br>• Acyclovir 800 mg per dose by mouth BID for 5 days<br>• Acyclovir 800 mg per dose by mouth TID for 2 days<br><br>**Note:** Consultation with an ophthalmologist experienced in managing herpes simplex infection involving the eye and its complications in children is strongly recommended when ocular disease is present. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | Acyclovir-Resistant HSV Infection<br>• Foscarnet 40 mg/kg body weight/dose given IV every 8 hours or 60 mg/kg body weight/dose IV every 12 hours should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/minute). | | |
| Histoplasmosis | Acute Primary Pulmonary Histoplasmosis<br>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth twice daily for 12 months. Duration of 12 weeks is sufficient for HIV-infected children, with functional cellular immunity (CD4 percentage >20% or if aged ≥6, CD4 cell count >300 cells/mm$^3$, provided monitoring confirms clinical improvement and decreased urine antigen concentrations. | Acute Primary Pulmonary Histoplasmosis<br>• Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily | Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules.<br><br>Urine antigen concentration should be assessed at diagnosis. If >39 ng/mL, serum concentrations should be followed. When serum levels become undetectable, urine concentrations should be monitored monthly during treatment and followed thereafter to identify relapse. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Mild Disseminated Disease<br>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth twice daily for 12 months | Mild Disseminated Disease<br>• Fluconazole 5–6 mg/kg body weight IV or by mouth (maximum 300 mg) per dose, twice daily (maximum 600 mg/day) for 12 months | Serum concentrations of itraconazole should be monitored and achieve a level of 1 µg/mL at steady-state. Levels exceeding 10 µg/mL should be followed by dose reduction.<br>High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered.<br>Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy.<br>Amphotericin B deoxycholate is better tolerated in children than in adults. Liposomal amphotericin B is preferred for treatment of parenchymal cerebral lesions. | |
| | Moderately Severe to Severe Disseminated Disease<br>*Acute Therapy (Minimum 2-Week Induction, Longer if Clinical Improvement is Delayed, Followed by Consolidation Therapy):*<br>• Liposomal amphotericin B 3–5 mg/kg body weight, IV once daily (preferred)<br>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative)<br>*Consolidation Therapy (Followed by Chronic Suppressive Therapy):*<br>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for 12 months | Moderately Severe to Severe Disseminated Disease<br>• If itraconazole not tolerated, amphotericin alone for 4–6 weeks can be used with monitoring that confirms decline in histoplasma urine and serum antigen levels.<br>• Liposomal amphotericin B 3–5 mg/kg body weight IV once daily (preferred) for 4–6 weeks<br>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) for 4–6 weeks | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Central Nervous System Infection<br>*Acute Therapy (4–6 Weeks, Followed by Consolidation Therapy)*<br>• Liposomal amphotericin B, 5 mg/kg body weight IV once daily (AII)<br>*Consolidation Therapy (Followed by Chronic Suppressive Therapy)*<br>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for ≥12 months and until histoplasma antigen is no longer detected in cerebrospinal fluid | | | |
| Human Papillomavirus (HPV) | • Podofilox solution/gel (0.5%) applied topically BID for 3 consecutive days a week up to 4 weeks (patient applied). Withhold treatment for 4 days and repeat the cycle weekly up to 4 times (BIII)<br>• Imiquimod cream (5%) applied topically at night and washed off in the morning for 3 non-consecutive nights a week for up to 16 weeks (patient applied) (BII) | • Intralesional IFN-α is generally not recommended because of high cost, difficult administration, and potential for systemic side effects (CIII)<br>• Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults that is commercially available through compounding pharmacies and has very limited use in children; systemic absorption can occur (CIII). | Adequate topical anesthetics to the genital area should be given before caustic modalities are applied.<br>Sexual contact should be limited while solutions or creams are on the skin.<br>Although sinecatechins (15% ointment) applied TID up to 16 weeks is recommended in immunocompetent individuals, data are insufficient on safety and efficacy in HIV-infected individuals. | November 6, 2013 |

# Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • TCA or BCA (80%–90%) applied topically weekly for up to 3 to 6 weeks (provider applied) (BIII)<br>• Podophyllin resin (10%–25% suspension in tincture of benzoin) applied topically and washed off several hours later, repeated weekly for 3 to 6 weeks (provider applied) (CIII)<br>• Cryotherapy with liquid nitrogen or cryoprobe applied every 1–2 weeks (BIII)<br>• Surgical removal either by tangential excision, tangential shave excision, curettage, or electrosurgery | • 5-FU/epinephrine gel implant should be offered in only severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects. | cART has not been consistently associated with reduced risk of HPV-related cervical abnormalities in HIV-infected women.<br><br>Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removing all disease.<br><br>For women who have exophytic cervical warts, a biopsy to exclude HSIL must be performed before treatment.<br><br>Liquid nitrogen or TCA/BCA is recommended for vaginal warts. Use of a cryoprobe in the vagina is not recommended.<br><br>Cryotherapy with liquid nitrogen or podophyllin resin (10%–25%) is recommended for urethral meatal warts.<br><br>Cryotherapy with liquid nitrogen or TCA/BCA or surgical removal is recommended for anal warts.<br><br>Abnormal Pap smear cytology should be referred to colposcopy for diagnosis and management. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Isosporiasis (Cystoisosporiasis) | TMP-SMX 5 mg/kg body weight of the TMP component (maximum 160 mg TMP) twice daily by mouth for 10 days | Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid 5–15 mg by mouth once daily for 14 days<br><br>Second-Line Alternatives<br>• Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth twice daily for 7 days<br>• Nitazoxanide (see doses below) for 3 consecutive days<br><br>*Children Aged 1 Year–3 Years*<br>• Nitazoxanide 100 mg by mouth every 12 hours<br><br>*Children Aged 4 Years–11 years*<br>• Nitazoxanide 200 mg by mouth every 12 hours<br><br>*Adolescents Aged ≥12 Years and Adults*<br>• Nitazoxanide 500 mg by mouth every 12 hours | If symptoms worsen or persist, the TMP-SMX dose (5 mg/kg/dose of the TMP component) may be given more frequently (e.g., 3–4 times daily by mouth for 10 days) and/or the duration of treatment may be increased to 3–4 weeks.<br><br>The optimal duration of treatment with pyrimethamine has not been established.<br><br>Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues. | February 8, 2019 |
| Malaria | Uncomplicated *P. Falciparum* or Unknown Malaria Species, from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region<br>• Atovaquone-proguanil (pediatric tablets 62.5 mg/25 mg; adult tablets 250 mg/100 mg), dosed once daily: | N/A | For quinine-based regimens, doxycycline or tetracycline should be used only in children aged ≥8 years. An alternative for children aged ≥8 years is clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours. Clindamycin should be used for children aged <8 years. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | o 5–8 kg; 2 pediatric tablets for 3 days;<br>o 9–10 kg; 3 pediatric tablets for 3 days;<br>o 11–20 kg; 4 pediatric tablets or 1 adult tablet for 3 days;<br>o 21–30 kg; 2 adult tablets for 3 days;<br>o 31–40 kg; 3 adult tablets for 3 days;<br>o >40 kg; 4 adult tablets for 3 days<br><br>Uncomplicated *P. Falciparum* OR Unknown Malaria Species from Chloroquine-Sensitive Region (See Comments for Link to Resistance Map)<br><br>• Chloroquine phosphate: 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1,000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2,500 mg] = 25 mg/kg body weight chloroquine base) | | Before primaquine is given, G6PD status **must** be verified. Primaquine may be given in combination with chloroquine if the G6PD status is known and negative, otherwise give after chloroquine (when G6PD status is available)<br><br>For most updated prevention and treatment recommendations for specific region, refer to updated CDC treatment table available at http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf<br><br>For sensitive and resistant malaria map: https://www.cdc.gov/malaria/travelers/country_table/a.html<br><br>High treatment failure rates due to chloroquine-resistant *P. vivax* have been documented in Papua New Guinea and Indonesia. Treatment should be selected from one of the three following options:<br><br>• Atovaquone-proguanil plus primaquine phosphate<br>• Quinine sulfate plus **either** doxycycline **or** tetracycline **plus** primaquine phosphate. This regimen cannot be used in children aged <8 years.<br>• Mefloquine plus primaquine phosphate | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | *P. vivax, P. ovale, P. malariae, P. knowlesi* (All Areas Except Papua New Guinea, Indonesia; See Comments)<br><br>*Initial Therapy (Followed by Anti-Relapse Therapy for* P. ovale *and* P. vivax*):*<br><br>• Chloroquine phosphate 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1,000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2,500 mg] = 25 mg/kg body weight chloroquine base)<br><br>*Anti-Relapse Therapy for* P. ovale and P. vivax*:*<br><br>• Primaquine 0.5 mg base/kg body weight (max 30 mg base) by mouth once daily for 14 days | | | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Uncomplicated *P. falciparum* or Unknown Malaria Species from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region<br>• Mefloquine (250-mg tablets only): 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth given 12 hours later<br>• Quinine sulfate 10 mg/kg body weight (maximum 650 mg) per dose by mouth every 8 hours for 3 to 7 days, **plus** Clindamycin 7 mg/kg body weight per dose by mouth every 8 hours for 7 days, **or** doxycycline: 2.2 mg/kg body weight per dose (maximum 100 mg) given by mouth every 12 hours, **or** tetracycline 6–12.5 mg/kg body weight per dose by mouth given every 6 hours (maximum dose: 500 mg per dose given 4 times daily) for 7 days. | | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Artemether-lumefantrine:<br>1 tablet = 20 mg Artemether and 120 mg lumefantrine, a 3-day treatment schedule for a total of 6 doses. The second dose follows the initial dose 8 hours later, then 1 dose twice daily for the next 2 days.<br>o 5 to <15 kg; 1 tablet per dose<br>o 15 to <25 kg; 2 tablets per dose<br>o 25 to <35 kg; 3 tablets per dose<br>o >35 kg; 4 tablets per dose | | | |
| Severe Malaria | • Quinidine gluconate 10 mg/kg body weight IV loading dose over 1–2 hours, then 0.02 mg/kg body weight/minute infusion for ≥24 hours (Treatment duration: 7 days in Southeast Asia, Oceania, otherwise 3 days)<br>*PLUS One of the Following:*<br>• Doxycycline 100 mg per dose by mouth every 12 hours for 7 days; for children <45 kg, use 2.2 mg/kg body weight per dose<br>OR<br>• Clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours for 7 days. | N/A | Quinidine gluconate is a class 1a anti-arrhythmic agent not typically stocked in pediatric hospitals. When regional supplies are unavailable, the CDC Malaria hotline may be of assistance (see below). Do not give quinidine gluconate as an IV bolus. Quinidine gluconate IV should be administered in a monitored setting. Cardiac monitoring required. Adverse events including severe hypoglycemia, prolongation of the QT interval, ventricular arrhythmia, and hypotension can result from the use of this drug at treatment doses. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | OR<br>• Tetracycline 6–12.5 mg/kg body weight per dose every 6 hours (maximum dose 500 mg per dose given 4 times daily) for 7 days<br>• Artesunate 2.4 mg/kg body weight IV bolus at 0, 12, 24, and 48 hours<br>*PLUS One of the Following:*<br>• Doxycycline (treatment dosing as above), or Atovaquone-proguanil (treatment dosing as above), *or*<br>• Mefloquine 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth once given 12 hours later, *or*<br>• Clindamycin (dosing as above) | | IND: IV artesunate is available from CDC. Contact the CDC Malaria Hotline at (770) 488-7788 from 8 a.m.–4:30 p.m. EST or (770) 488-7100 after hours, weekends, and holidays. Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), clindamycin, mefloquine, or (for children aged >8 years) doxycycline.<br>Quinidine gluconate: 10 mg = 6.25 mg quinidine base.<br>Doxycycline (or tetracycline) should be used in children aged >8 years. For patients unable to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline. For children >45 kg, use the same dosing as per adults. For IV use, avoid rapid administration.<br>For patients unable to take oral clindamycin, give 10 mg base/kg loading dose IV, followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as a patient can take oral medication. For IV use, avoid rapid administration.<br>*Drug Interactions*<br>• Avoid co-administration of quinidine with ritonavir | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | | • Use quinidine with caution with other protease inhibitors. | |
| Microsporidiosis | Effective ART Therapy<br>• Immune reconstitution may lead to microbiologic and clinical response.<br><br>For Disseminated (Not Ocular) and Intestinal Infection Attributed to Microsporidia Other than *E. bieneusi* or *V. corneae*—<br>• Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily (in addition to ART)<br><br>*Treatment Duration*<br>• Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms<br><br>For *E. bieneusi* or *V. corneae* Infections—<br>• Fumagillin (where available) adult dose 20 mg by mouth 3 times daily, *or* | N/A | • Supportive care (e.g., hydration, correction of electrolyte abnormalities, nutritional support)<br>• Fumagillin for systemic use is unavailable in the United States and data on dosing in children are unavailable. Consultation with an expert is recommended. | December 15, 2016 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • TNP-470 (a synthetic analogue of fumagillin; where available) recommended for treatment of infections caused by *E. bieneusi* in HIV-infected adults (in addition to ART)<br><br>For Ocular Infection—<br><br>• Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops QID (investigational use only in United States) **plus**, for microsporidial infection other than *E. bieneusi* and *V. corneae*, albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily for management of systemic infection in systemic infection (in addition to ART)<br><br>*Treatment Duration*<br><br>• Continue until sustained immune reconstitution (longer than 6 months at CDC immunologic category 1 or 2) after initiation of ART and resolution of signs and symptoms. | | | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| *Mycobacterium avium* Complex (MAC) | **Initial Treatment (≥2 Drugs)**<br><br>• Clarithromycin 7.5–15 mg/kg body weight (maximum 500 mg/dose) orally twice daily **plus** ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) orally once daily followed by chronic suppressive therapy<br><br>*For Severe Disease, Add—*<br><br>• Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) orally once daily | *If Intolerant to Clarithromycin—*<br><br>• Azithromycin 10–12 mg/kg body weight (maximum 500 mg/day) orally once daily<br><br>*If Rifabutin Cannot Be Administered and a Third Drug is Needed in Addition to a Macrolide and Ethambutol, or if a Fourth Drug is Needed in Addition to Rifabutin for Patients with More Severe Symptoms or Disseminated Disease—*<br><br>• Ciprofloxacin 10–15 mg/kg orally twice daily (maximum 1.5 g/day), *or*<br><br>• Levofloxacin 500 mg orally once daily, *or*<br><br>• Amikacin 15–30 mg/kg body weight IV in 1 or 2 divided doses (maximum 1.5 g/day) | Combination therapy with a minimum of 2 drugs is recommended for ≥12 months.<br><br>Clofazimine is associated with increased mortality in adults with HIV infection and should not be used.<br><br>Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination.<br><br>Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are not labeled for use in children aged <18 years because of concerns regarding potential effects on cartilage; use in children aged <18 years requires an assessment of potential risks and benefits<br><br>Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. | January 8, 2019 |
| *Mycobacterium tuberculosis* | Intrathoracic Disease<br><br>*Drug-Susceptible TB*<br><br>• Intensive Phase (2 Months)<br>  o Isoniazid, 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus** | Alternative for Rifampin<br><br>• Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if three times a week)<br><br>• Discuss with an expert. | Treatment for TB disease should always be provided by DOT.<br><br>If ART-naive, start TB therapy immediately and initiate ART within 2–8 weeks. | September 14, 2023 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily, **plus**<br>o Pyrazinamide 30–40 mg/kg body weight (maximum 2,000 mg/day) by mouth once daily, **plus**<br>o Ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) by mouth once daily<br>o In children with minimal disease with fully drug-susceptible TB, some experts recommend a three-drug intensive phase regimen excluding ethambutol.<br>• Continuation Phase (4 Months)<br>o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus**<br>o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily<br>Extrathoracic Disease<br>Note: Depends on disease entity<br>• Lymph node TB—treat as minimal intrathoracic disease | Alternative Continuation Phase with Three Times Weekly Dosing (4 Months)<br>*If Good Adherence and Treatment Response*<br>• Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth three times per week, **plus**<br>• Rifampin 15–20 mg/kg body weight (maximum 600 mg/day) three times per week<br>• In children with minimal disease with fully drug-susceptible TB, some experts recommend a continuation phase of 4 months (total duration of therapy of 6 months) | If already on ART, review regimen to minimize potential toxicities and drug interactions; start TB treatment immediately.<br>Potential drug toxicity and interactions should be reviewed at every visit. Drug interactions with ART should be considered for all rifamycin-containing alternatives.<br>Adjunctive Treatment<br>• Co-trimoxazole prophylaxis<br>• Pyridoxine 1–2 mg/kg body weight/day (maximum 25–50 mg/day) with isoniazid or cycloserine/terizidone, if malnourished. Pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all children with HIV; and pregnant adolescents and people.<br>• Corticosteroids (2 mg/kg body weight per day of prednisone [maximum 60 mg/day] or its equivalent for 4–6 weeks followed by tapering) with TB meningitis; may be considered with pleural effusions, pericarditis, severe airway compression, or severe IRIS. | |

**Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations**

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Bone or joint disease—consider extending the continuation phase to 10 months (for total duration of therapy of 12 months).<br><br>TB Meningitis<br><br>• As an alternative to ethambutol or streptomycin, 20–40 mg/kg body weight (maximum 1 g/day) IM once daily. During intensive phase, consider ethionamide, 15–20 mg/kg body weight by mouth (maximum 1 g/day), initially divided into two doses until well tolerated.<br><br>• Many experts recommend rifampin doses of 22.5–30 mg/kg daily for treatment of TB meningitis. See the AAP Red Book and WHO Operational Handbook on Tuberculosis for more information.<br><br>• Consider extending the continuation phase to 10 months (for a total duration of therapy of 12 months).<br><br>• Discuss with an expert. | | Second-Line Drug Doses<br><br>• Consult with an expert as dosing guidelines continue to evolve with emerging data.<br><br>[a] Some experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers. | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Drug-Resistant TB<br>• Therapy should be based on the resistance pattern of the child (or of the source case where the child's isolate is not available); consult an expert. | | | |
| *Pneumocystis* Pneumonia | TMP-SMX 3.75–5 mg/kg body weight/dose TMP (based on TMP component) every 6 hours IV or orally given for 21 days (followed by secondary prophylaxis dosing) | If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy<br>*Pentamidine*<br>• 4 mg/kg body weight/dose IV/IM once daily is the first-choice alternative regimen. **Note:** Pentamidine can be changed to atovaquone after 7–10 days IV therapy.<br>Atovaquone<br>*Daily Dosing*<br>• *Children aged 1–3 months and >24 months–12 years:* 30–40 mg/kg body weight/dose by mouth once daily with food<br>• *Children aged 4–24 months:* 45 mg/kg body weight/dose by mouth once daily with food<br>*Twice-Daily Dosing**<br>• *Children aged ≥13 years:* 750 mg/dose by mouth twice daily | After acute pneumonitis resolved in mild-moderate disease, IV TMP-SMX can be changed to oral. For oral administration, total daily dose of TMP-SMX can also be administered in 3 divided doses (every 8 hours).<br>Dapsone 2 mg/kg body weight by mouth once daily (maximum 100 mg/day) **plus** trimethoprim 5 mg/kg body weight by mouth every 8 hours has been used in adults but data in children are limited.<br>Primaquine base 0.3 mg/kg body weight by mouth once daily (maximum 30 mg/day) **plus** clindamycin 10 mg/kg body weight/dose IV or by mouth (maximum 600 mg given IV and 300–450 mg given orally) every 6 hours has been used in adults, but data in children are not available.<br>Indications for Corticosteroids<br>• $PaO_2$ <70 mm Hg at room air or alveolar-arterial oxygen gradient >35 mm Hg | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | | • * Some experts use twice-daily dosing of atovaquone as alternative treatment for PCP in children aged <12 years:<br>• *Children aged 1–3 months and >24 months to 12 years:* 15–20 mg/kg body weight /dose by mouth twice daily with food<br>• *Children aged 4–24 months:* 22.5 mg/kg body weight/dose by mouth twice daily with food. | *Prednisone Dose*<br>• 1 mg/kg body weight/dose by mouth twice daily for 5 days, then<br>• 0.5–1 mg/kg body weight/dose by mouth twice daily for 5 days, then<br>• 0.5 mg/kg body weight by mouth once daily for days 11 to 21.<br>*Alternative Corticosteroid Regimens Include—*<br>• Adult dosage of prednisone: 40 mg/dose twice daily on days 1–5, 40 mg/dose once daily on days 6–10, 20 mg/dose once daily on days 11–21, and<br>• Methylprednisolone IV 1 mg/kg/dose every 6 hours on days 1–7, 1 mg/kg/dose twice daily on days 8–9, 0.5 mg/kg/dose twice daily on days 10 and 11, and 1 mg/kg/dose once daily on days 12–16.<br>Chronic suppressive therapy (secondary prophylaxis) with TMP/SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis). | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Syphilis | Congenital<br>*Proven or Highly Probable Disease*<br>• Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 12 hours for the first 7 days of life, and then every 8 hours for 10 days<br>• If diagnosed after 1 month of age, aqueous penicillin G 200,000–300,000 unit/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10 days<br>*Possible Disease*<br>• Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010. | Congenital<br>*Proven or Highly Probable Disease (Less Desirable if CNS Involvement)*<br>• Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days<br>*Possible Disease*<br>• Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer, and test results. Scenarios that include variations of these factors are described and treatment recommendations are provided in detail on pages 36–37 of the Centers for Disease Control STD Treatment Guidelines, 2010. | For treatment of congenital syphilis, repeat the entire course of treatment if >1 day of treatment is missed.<br>Examinations and serologic testing for children with congenital syphilis should occur every 2–3 months until the test becomes non-reactive or there is a fourfold decrease in titer. Children with increasing titers or persistently positive titers (even if low levels) at ages 6–12 months should be evaluated and considered for re-treatment.<br>In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable.<br>Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | Acquired<br>*Early Stage (Primary, Secondary, Early Latent)*<br>• Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM for 1 dose<br>*Late Latent*<br>• Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM once weekly for 3 doses<br>*Neurosyphilis (Including Ocular)*<br>• Aqueous penicillin G 200,000–300,000 units/kg body weight per day administered as 50,000 units/kg body weight per dose IV every 4–6 hours (maximum 18–24 million units per day) for 10–14 days | | | |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| Toxoplasmosis | Congenital Toxoplasmosis<br>• Pyrimethamine loading dose–2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, **plus**<br>• Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, **plus**<br>• Sulfadiazine 50 mg/kg body weight by mouth twice daily<br>*Treatment Duration:*<br>• 12 months<br>Acquired Toxoplasmosis<br>*Acute Induction Therapy (Followed by Chronic Suppressive Therapy)*<br>• Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, **plus**<br>• Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, **plus** | For Sulfonamide-Intolerant Patients—<br>• Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin | Congenital Toxoplasmosis<br>• For infants born to mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy.<br>Acquired Toxoplasmosis<br>• Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing.<br>• TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children.<br>• Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children. | November 6, 2013 |

## Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy<br><br>*Treatment Duration (Followed by Chronic Suppressive Therapy)*<br><br>• ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks) | | • Azithromycin (for adults, 900–1,200 mg/day, corresponding to 20 mg/kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children.<br><br>• Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible.<br><br>• Anticonvulsants should be administered to patients with a history of seizures and continued through the acute treatment; but should not be used prophylactically. | |
| Varicella-Zoster Virus (VZV) | Varicella<br><br>*Children with No or Moderate Immune Suppression (CDC Immunologic Categories 1 and 2) and Mild Varicella Disease*<br><br>• Acyclovir 20 mg/kg body weight/dose by mouth (maximum 800 mg/dose) four times a day for 7–10 days and until no new lesions for 48 hours<br><br>*Children with Severe Immune Suppression or Severe Varicella Disease (see text)* | Patients Unresponsive to Acyclovir<br><br>• Foscarnet (40–60 mg/kg body weight/dose IV every 8 hours) for 7–10 days or until no new lesions have appeared for 48 hours | In children aged ≥1 year, some experts base IV acyclovir dosing on body surface area (500 mg/$m^2$ body surface area/dose IV every 8 hours) instead of body weight.<br><br>Valacyclovir is approved for use in adults and adolescents with zoster at 1 g/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. Valacyclovir can be used in children at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day. Doses lower than this may be insufficient for children weighing <20 kg. There is no | December 9, 2019 |

# Table 3. Treatment of Opportunistic Infections in Children with and Exposed to HIV—Summary of Recommendations

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | • Acyclovir 10 mg/kg body weight or 500 mg/m²/dose IV every 8 hours for 7–10 days and until no new lesions for 48 hours<br><br>Zoster<br><br>*Children with Uncomplicated Zoster and No or Moderate Immune Suppression*<br><br>• Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth four times a day for 7–10 days.<br><br>*Children with Severe Immunosuppression (CDC Immunologic Category 3), Trigeminal or Sacral Nerve Involvement, Extensive Multidermatomal, or Disseminated Zoster*<br><br>• Acyclovir 10 mg/kg body weight/dose or 500 mg/m² IV every 8 hours until cutaneous lesions and visceral disease are clearly resolving, then can switch to oral acyclovir to complete a 10–14-day course | | pediatric preparation, although 500-mg capsules can be extemporaneously compounded to make a suspension to administer valacyclovir 20 mg/kg body weight/dose (maximum dose 1 g) given three times a day (see prescribing information).<br><br>Famciclovir is approved for use in adults and adolescents with zoster at 500 mg/dose by mouth three times a day for 7 days; the same dose has been used for varicella infections. A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation. A schedule for weight-adjusted dosing is available to inform dosing of small children.<br><br>Involvement of an ophthalmologist with experience in managing HZ ophthalmicus and its complications in children **is strongly recommended** when ocular involvement is evident.<br><br>Optimal management of progressive outer retinal necrosis has not been defined. | |

| Indication | First Choice | Alternative | Comments/Special Issues | Last Reviewed |
|---|---|---|---|---|
| | *Children with Progressive Outer Retinal Necrosis*<br>• Acyclovir (10 mg/kg or 500 mg/m$^2$ every 8 hours) or ganciclovir 5 mg/kg body weight/dose IV every 12 hours, **plus**<br>• Foscarnet 90 mg/kg body weight/dose IV every 12 hours, **plus**<br>• Ganciclovir 2 mg/0.05 mL intravitreal injection twice weekly and/or foscarnet 1.2 mg/0.05 mL intravitreal injection twice weekly<br>*Children with Acute Retinal Necrosis*<br>• Acyclovir 10–15 mg/kg body weight/dose IV every 8 hours daily for 10–14 days, **followed by** oral valacyclovir 1 g/dose three times a day for 4–6 weeks (for children old enough to receive adult dose).<br>• Alternative to oral valacyclovir is oral acyclovir 20 mg/kg body weight/dose four times a day for 4–6 weeks. | | | |

**Key:** AAP = American Academy of Pediatrics; ART = antiretroviral therapy; BCA = bicholoracetic acid; BID = twice daily; BSA = body surface area; cART = combination antiretroviral therapy; CNS = central nervous system; CrCl = (estimated) creatinine clearance; CSF = cerebrospinal fluid; DOT = directly observed therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; ICP = intracranial pressure; IFN = interferon; IFN-α = interferon alpha; IGRA = interferon-gamma release assay; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LIP = lymphocytic interstitial pneumonia; PCP = pneumocystis pneumonia; PCR = polymerase chain reaction; PK = pharmacokinetic; QID = four times daily; SQ = subcutaneous; TB = tuberculosis; TCA = trichloroacetic acid; TE = toxoplasmic encephalitis; TID = three times daily; TMP-SMX = trimethoprim-sulfamethoxazole; WHO = World Health Organization

## Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities (Last updated November 6, 2013; last reviewed November 6, 2013) (page 1 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Acyclovir** (Zovirax) | Oral Suspension:<br>• 40 mg/mL<br>Capsules:<br>• 200 mg<br>Tablets:<br>• 400 mg<br>• 800 mg<br>IV | More Frequent:<br>• Phlebitis (at injection site when given IV)<br>Less Frequent:<br>• Acute renal failure (parenteral use, more common with rapid infusion)<br>Rare<br>*Parenteral Form Only:*<br>• Encephalopathy<br>• Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia, hemolysis)<br>• Crystalluria, hematuria<br>• Disseminated intravascular coagulation<br>• Hypotension<br>• Neuropsychiatric toxicity (with high doses)<br>Parenteral and Oral Forms:<br>• Rash (urticarial, exfoliative skin disorders including SJS)<br>• Anaphylaxis<br>• Seizures<br>• Elevated transaminase enzymes<br>• Fever, hallucinations<br>• Leukopenia<br>• Lymphadenopathy<br>• Peripheral edema<br>• Visual abnormalities | More Frequent:<br>• GI disturbances (anorexia, diarrhea, nausea, vomiting)<br>• Headache, lightheadedness<br>• Malaise<br>Less Frequent (More Marked in Older Adults):<br>• Agitation<br>• Alopecia<br>• Dizziness<br>• Myalgia, paresthesia<br>• Somnolence | Requires dose adjustment in patients with renal impairment.<br>Avoid other nephrotoxic drugs.<br>Administer IV preparation by slow IV infusion over at least 1 hour at a final concentration not to exceed 7 mg/mL. This is to avoid renal tubular damage related to crystalluria; must be accompanied by adequate hydration. |
| **Albendazole** (Albenza) | Tablets:<br>• 200 mg | More Frequent:<br>• Abnormal liver function tests (LFTs)<br>Less Frequent:<br>• Hypersensitivity (rash, pruritus)<br>• Neutropenia (with high doses)<br>Rare:<br>• Pancytopenia | Less frequent:<br>• CNS effects (dizziness, headache)<br>• GI disturbances (abdominal pain, diarrhea, nausea, vomiting)<br>Rare:<br>• Alopecia | Should be given with food.<br>May crush or chew tablets and give with water.<br>Monitor CBC and LFTs prior to each cycle. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 2 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Amikacin** | IV | More Frequent:<br>• Nephrotoxicity<br>• Neurotoxicity (including muscle twitching, seizures)<br>• Ototoxicity, both auditory and vestibular<br>Less Frequent:<br>• Hypersensitivity (skin rash, redness, or swelling)<br>Rare:<br>• Neuromuscular blockade | N/A | Must be infused over 30 to 60 minutes to avoid neuromuscular blockade.<br>Requires dose adjustment in patients with impaired renal function.<br>Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy.<br>Therapeutic drug monitoring (TDM). indicated |
| **Amphotericin B Deoxycholate** (Fungizone) | IV | More Frequent:<br>• Infusion-related reactions (fever/chills; nausea/vomiting; hypotension; anaphylaxis)<br>• Anemia<br>• Hypokalemia<br>• Renal function impairment<br>• Thrombophlebitis (at injection site)<br>Less Frequent or Rare:<br>• Blurred or double vision<br>• Cardiac arrhythmias, usually with rapid infusions<br>• Hypersensitivity (rash)<br>• Leukopenia<br>• Polyneuropathy<br>• Seizures<br>• Thrombocytopenia | • GI disturbance (nausea, vomiting, diarrhea, abdominal pain)<br>• Headache | Monitor BUN, Cr, CBC, electrolytes, LFTs.<br>Infuse over 1 to 2 hours; in patients with azotemia, hyperkalemia, or getting doses >1 mg/kg, infuse over 3 to 6 hours.<br>Requires dose reduction in patients with impaired renal function.<br>Avoid other nephrotoxic drugs, when possible,because nephrotoxicity is exacerbated with concomitant use of other nephrotoxic drugs; permanent nephrotoxicity is related to cumulative dose.<br>Nephrotoxicity may be ameliorated by hydration with 0.9% saline IV over 30 minutes prior to the amphotericin B infusion.<br>Infusion-related reactions less frequent in children than adults; the onset is usually 1 to 3 hours after infusion, duration <1 hour; frequency decreases over time.<br>Pre-treatment with acetaminophen and/or diphenhydramine may alleviate febrile reactions. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 3 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Amphotericin B Lipid Complex** (Abelcet) | IV | More Frequent:<br>• Infusion-related reactions (fever/chills, nausea/ vomiting; headache, nausea and vomiting)<br>Less Frequent:<br>• Anemia<br>• Leukopenia<br>• Respiratory distress<br>• Thrombocytopenia<br>• Renal function impairment | • GI disturbance (loss of appetite, nausea, vomiting, diarrhea, abdominal pain) | Monitor BUN, Cr, CBC, electrolytes, and LFTs.<br>Infuse diluted solution at rate of 2.5 mg/kg/hour.<br>In-line filters should not be used.<br>Use with caution with other drugs that are bone marrow suppressants or that are nephrotoxic; renal toxicity is dose-dependent, but less renal toxicity than seen with conventional amphotericin B.<br>Consider dose reduction in patients with impaired renal function. |
| **Amphotericin B Liposome** (AmBisome) | IV | More Frequent:<br>• Fever, chills<br>• Hypokalemia<br>Less Frequent:<br>• Back pain<br>• Chest pain<br>• Dark urine<br>• Dyspnea<br>• Infusion-related reaction (fever/chills, headache)<br>• Jaundice<br>• Renal function impairment<br>Rare:<br>• Anaphylactic reaction | • GI disturbance (nausea, vomiting, diarrhea, abdominal pain)<br>• Headache<br>• Skin rash | Monitor BUN, Cr, CBC, electrolytes, and LFTs.<br>Infuse over 2 hours.<br>Consider dose reduction in patients with impaired renal function. |
| **Artesunate** | IV:<br>• Only available from CDC Malaria Hotline; telephone: (770) 488-7788 | Rare:<br>• Anaphylactic reaction<br>• Neutropenia<br>• Bradycardia | • GI disturbance (nausea, vomiting)<br>• Headache<br>• Skin rash | Monitor CBC, LFTs, and electrolytes.<br>~40% less mortality than with quinidine use in severe malaria<br>50% lower incidence of hypoglycemia than quinidine |
| **Atovaquone** (Mepron) | Oral Suspension:<br>• 150 mg/mL | Frequent:<br>• Fever<br>• Skin rash | Frequent:<br>• GI disturbances (nausea, vomiting, diarrhea)<br>• Headache<br>• Cough<br>• Insomnia | Should be administered with a meal to enhance absorption; bioavailability increases 3-fold when administered with high-fat meal. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 4 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Atovaquone/ Proguanil** (Malarone) | Tablets:<br>• Pediatric tablets; 62.5 mg/ 25 mg<br>• Adult tablets; 250 mg/100 mg | Less frequent:<br>• Vomiting<br>• Pruritus | N/A | Pediatric tablets are available to make dosing easier.<br>Side effects requiring discontinuation in ~1%–2% of patients<br>Not recommended for prophylaxis in patients with CrCl <30 mL/min. |
| **Azithromycin** (Zithromax) | Oral Suspension:<br>• 20 mg/mL<br>• 40 mg/mL<br>Tablets:<br>• 250 mg<br>• 500 mg<br>• 600 mg<br>IV | More Frequent:<br>• Thrombophlebitis (IV form)<br>Rare:<br>• Acute interstitial nephritis<br>• Allergic reactions/ anaphylaxis (dyspnea, hives, rash)<br>• Pseudomembranous colitis | • GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting)<br>• Dizziness, headache | Administer 1 hour before or 2 hours after a meal; do not administer with aluminum- and magnesium-containing antacids.<br>IV should be infused at concentration of 1 mg/mL over a 3-hour period, or 2 mg/mL over a 1-hour period; should not be administered as a bolus.<br>Use with caution in patients with hepatic function impairment; biliary excretion is the main route of elimination.<br>Potential drug interactions. |
| **Capreomycin** (Capastat) | IM | More Frequent:<br>• Nephrotoxicity<br>Less Frequent:<br>• Hypersensitivity (rash, fever)<br>• Hypokalemia<br>• Neuromuscular blockade<br>• Ototoxicity, both auditory and vestibular<br>• Injection site pain, sterile abscess | N/A | Requires dose adjustment in patients with impaired renal function.<br>Administer only by deep IM injection into large muscle mass (superficial injections may result in sterile abscess).<br>Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy.<br>Monitor LFTs and electrolytes. |
| **Caspofungin** (Cancidas) | IV | More Frequent:<br>• Histamine-mediated symptoms (fever, facial swelling, pruritus, bronchospasm)<br>Rare:<br>• Hypokalemia<br>• Anaphylactic reaction | • GI disturbances (nausea, vomiting, diarrhea)<br>• Headache<br>• Skin rash, facial flushing<br>• Elevated liver transaminases<br>• Thrombophlebitis | Requires dose adjustment in moderate-to-severe hepatic insufficiency.<br>IV infusion over 1 hour in normal saline (do not use diluents containing dextrose) |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 5 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Chloroquine Phosphate** (Aralen) | Tablets:<br>• 500 mg<br>• 250 mg | More Frequent:<br>• Pruritus: Common in individuals of black race (25%–33%)<br>Less Frequent, but More Severe:<br>• Auditory toxicity<br>• Ocular toxicity<br>• Neuropsychiatric disorders<br>• QT prolongation<br>• Hepatitis<br>• Bone marrow suppression<br>• Peripheral neuropathy | • Psoriasis exacerbations<br>• GI disturbances (nausea, vomiting, diarrhea)<br>• Visual disturbances including photosensitivity<br>• Tinnitus<br>• Muscle weakness | Store in child-proof containers and protect from light.<br>Can be toxic in overdose.<br>Bitter tasting, so consider administering with foods that can mask the taste.<br>Solution available worldwide, but not in United States.<br>Caution in patients with G6PD deficiency or seizure disorder.<br>Monitor CBC; periodic neurologic and ophthalmologic exams in patients on prolonged therapy. |
| **Cidofovir** (Vistide) | IV | More Frequent:<br>• Nephrotoxicity<br>• Neutropenia<br>Less Frequent:<br>• Fever and allergic reactions<br>Rare:<br>• Vision changes due to ocular hypotony<br>• Metabolic acidosis | • GI disturbances (anorexia, diarrhea, nausea, vomiting)<br>• Headache<br>• Asthenia<br>• Proteinuria | Infuse over 1 hour.<br>Should not be used in patients with severe renal impairment.<br>Nephrotoxicity risk is decreased with pre-hydration with IV normal saline and probenecid with each infusion. Probenecid is administered prior to each dose and repeated for two additional doses after infusion. Additional hydration after infusion is recommended if tolerated.<br>Concurrent use of other nephro-toxic drugs should be avoided.<br>Monitor renal function, urinalysis, electrolytes, and CBC and perform ophthalmologic exams. |
| **Ciprofloxacin** (Cipro) | Oral Suspension:<br>• 50 mg/mL<br>• 100 mg/mL<br>Tablets:<br>• 100 mg<br>• 250 mg<br>• 500 mg<br>• 750 mg<br>XR Tablets<br>*Cipro XR:*<br>• 500 mg<br>• 1000 mg<br>*Proquin XR:*<br>• 500 mg<br>IV | Less Frequent:<br>• Phototoxicity<br>Rare:<br>• CNS stimulation<br>• Hepatotoxicity<br>• Hypersensitivity reactions (rash, pruritus, and exfoliative skin disorders including SJS, dyspnea, and vasculitis)<br>• Interstitial nephritis<br>• Phlebitis (at injection sites)<br>• Pseudomembranous colitis<br>• Tendonitis or tendon rupture<br>• QT interval prolongation | More Frequent:<br>• GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting)<br>• CNS toxicity (dizziness, headache, insomnia, drowsiness)<br>Less Frequent:<br>• Change in taste<br>• Photosensitivity | Administer oral formulations at least 2 hours before, or 6 hours after, sucralfate or antacids or other products containing calcium, zinc, or iron (including daily products or calcium-fortified juices). Take with full glass of water to avoid crystalluria.<br>Possible phototoxicity reactions with sun exposure.<br>IV infusions should be over 1 hour.<br>Do not split, crush, or chew extended-release tablets. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 6 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Clarithromycin** (Biaxin) | Oral Suspension:<br>• 25 mg/mL<br>• 50 mg/mL<br>Tablets:<br>• 250 mg<br>• 500 mg | Rare:<br>• Hepatotoxicity<br>• Hypersensitivity reaction (rash, pruritus, dyspnea)<br>• Pseudomembranous colitis<br>• Thrombocytopenia<br>• QT interval prolongation | More Frequent:<br>• GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting)<br>Less Frequent:<br>• Abnormal taste sensation<br>• Headache<br>• Rash | Requires dose adjustment in patients with impaired renal function.<br>Can be administered without regard to meals.<br>Reconstituted suspension should not be refrigerated.<br>Potential drug interactions |
| **Clindamycin** (Cleocin) | Oral Solution:<br>• 15 mg/mL<br>Capsules:<br>• 75 mg, 150 mg, 300 mg<br>IV | More Frequent:<br>• Pseudomembranous colitis<br>Less Frequent:<br>• Hypersensitivity (skin rash, redness, pruritus)<br>• Neutropenia<br>• Thrombocytopenia | More Frequent:<br>• GI disturbances (abdominal pain, nausea, vomiting, diarrhea)<br>Less Frequent:<br>• Fungal overgrowth, rectal and genital areas | IV preparation contains benzyl alcohol, not recommended for use in neonates.<br>IV preparation must be diluted prior to administration.<br>Capsule formulation should be taken with food or a full glass of water to avoid esophageal irritation.<br>Reconstituted oral solution should not be refrigerated. |
| **Cycloserine** (Seromycin) | Capsules:<br>• 250 mg | More Frequent:<br>• CNS toxicity (including confusion, anxiety)<br>Less Frequent:<br>• Hypersensitivity (skin rash)<br>• Peripheral neuropathy<br>• Seizures<br>• Psychosis<br>Rare:<br>• Cardiac arrhythmias | • Headache, dizziness, drowsiness, confusion<br>Rare:<br>• Photosensitivity | Take with food to minimize gastric irritation.<br>Neurotoxicity is related to excessive serum concentrations; serum concentrations should be maintained at 25–30 mcg/mL.<br>Requires dose adjustment in patients with impaired renal function.<br>Do not administer to patients with severe renal impairment (because of increased risk of neurotoxicity).<br>Should monitor serum levels, if possible.<br>Should administer pyridoxine at the same time.<br>Monitor renal function, LFTs, and CBC. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 7 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Dapsone** | Syrup (available under Compassionate Use IND):<br>• 2 mg/mL<br>Tablets:<br>• 25 mg<br>• 100 mg | More Frequent:<br>• Hemolytic anemia (especially if G6PD deficiency)<br>• Methemoglobinemia<br>• Skin rash<br>Rare:<br>• Blood dyscrasias<br>• Exfoliative skin disorders (including SJS)<br>• Hepatic toxicity<br>• Mood or other mental changes<br>• Peripheral neuritis<br>• Hypersensitivity reaction (fever, rash, jaundice, anemia) | • CNS toxicity (headache, insomnia, nervousness)<br>• GI disturbances (anorexia, nausea, vomiting)<br>• Photosensitivity reactions | Protect from light; dispense syrup in amber glass bottles.<br>Monitor CBC and LFTs. |
| **Doxycycline** (Vibramycin) | Tablets and Capsules:<br>• 20 mg<br>• 50 mg<br>• 75 mg<br>• 100 mg<br>Oral Suspension and Syrup:<br>• 5 mg/mL oral suspension<br>• 10 mg/mL oral syrup<br>IV | More Frequent:<br>• GI irritation, pill esophagitis<br>• Photosensitivity<br>Less frequent:<br>• May cause increased intracranial pressure, photosensitivity, hemolytic anemia, rash, and hypersensitivity reactions.<br>• *Clostridium difficile*-associated diarrhea<br>• Pseudotumor cerebri | • Staining of teeth a concern for individuals aged <8 years<br>• Photo-onycholysis<br>• GI disturbances (nausea, vomiting, abdominal cramps) | Swallow with adequate amounts of fluids<br>Avoid antacids, milk, dairy products, and iron for 1 hour before or 2 hours after administration of doxycycline.<br>Use with caution in hepatic and renal disease.<br>IV doses should be infused over 1 to 4 hours.<br>Patient should avoid prolonged exposure to direct sunlight (skin sensitivity).<br>Generally not recommended for use in children aged <8 years because of risk of tooth enamel hypoplasia and discoloration, unless benefit outweighs risk.<br>Monitor renal function, CBC, and LFTs if prolonged therapy. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 8 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Erythromycin** | Erythromycin-Base Tablet:<br>• 250 mg<br>• 333 mg<br>• 500 mg<br>Delayed-Release Tablet:<br>• 250 mg<br>• 333 mg<br>• 500 mg<br>Delayed-Release Capsule:<br>• 250 mg<br>Erythromycin Ethyl Succinate<br>*Suspension:*<br>• 200 mg<br>• 400 mg/5 mL<br>*Oral Drops:*<br>• 100 mg/2.5 mL<br>*Chewable Tablet:*<br>• 200 mg<br>*Tablet:*<br>• 400 mg<br>Erythromycin Estolate<br>*Suspension:*<br>• 125 mg<br>• 250 mg/5 mL<br>Erythromycin Stearate<br>*Tablet:*<br>• 250 mg<br>• 500 mg<br>Erythromycin Gluceptate:<br>• IV<br>Erythromycin Lactobionate:<br>• IV | Less Frequent:<br>• Estolate may cause cholestatic jaundice, although hepatotoxicity is uncommon (2% of reported cases).<br>Rare:<br>• QT prolongation<br>• Hypersensitivity reactions (rash, exfoliative skin disorders including SJS) | • GI disturbances (nausea, vomiting, abdominal cramps)<br>• Rash, urticaria<br>• Increased LFTs | Use with caution in liver disease.<br>Oral therapy should replace IV therapy as soon as possible.<br>Give oral doses after meals.<br>Parenteral administration should consist of a continuous drip or slow infusion over 1 hour or longer.<br>Adjust dose in renal failure.<br>Erythromycin should be used with caution in neonates; hypertrophic pyloric stenosis and life-threatening episodes of ventricular tachycardia associated with prolonged QTc interval have been reported.<br>High potential for interaction with many ARVs and other drugs. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 9 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Ethambutol** (Myambutol) | Tablets:<br>• 100 mg<br>• 400 mg | Less Frequent:<br>• Acute gouty arthritis (secondary to hyperuricemia)<br>Rare:<br>• Hypersensitivity (rash, fever, joint pain)<br>• Peripheral neuropathy<br>• Retrobulbar optic neuritis, decreased visual acuity, loss of red-green color discrimination<br>• Bone marrow suppression<br>• Abnormal LFTs, hepatotoxicity | • GI disturbances (abdominal pain, anorexia, nausea, vomiting)<br>• Confusion<br>• Disorientation<br>• Headache | Requires dose adjustment in patients with impaired renal function.<br>Take with food to minimize gastric irritation.<br>Monitor visual acuity and red-green color discrimination regularly.<br>Monitor renal function, LFTs, and CBC.<br>Avoid concomitant use of drugs with neurotoxicity. |
| **Ethionamide** (Trecator-SC) | Tablets:<br>• 250 mg | Less Frequent:<br>• Hepatitis, jaundice<br>• Peripheral neuritis<br>• Psychiatric disturbances<br>Rare:<br>• Goiter or hypothyroidism<br>• Hypoglycemia<br>• Optic neuritis<br>• Skin rash | More Frequent:<br>• GI disturbances (anorexia, metallic taste, nausea, vomiting, stomatitis)<br>• Orthostatic hypotension<br>Rare:<br>• Gynecomastia | Avoid use of other neurotoxic drugs that could increase potential for peripheral neuropathy and optic neuritis.<br>Administration of pyridoxine may alleviate peripheral neuritis.<br>Take with food to minimize gastric irritation.<br>Monitor LFTs, glucose, and thyroid function. Perform periodic ophthalmologic exams. |
| **Fluconazole** (Diflucan) | Oral Suspension:<br>• 10 mg/mL<br>• 40 mg/mL<br>Tablets:<br>• 50 mg<br>• 100 mg<br>• 150 mg<br>• 200 mg<br>IV | Less Frequent:<br>• Hypersensitivity (fever, chills, skin rash)<br>Rare:<br>• Agranulocytosis, eosinophilia, leucopenia, thrombocytopenia<br>• Exfoliative skin disorders (including SJS)<br>• Hepatotoxicity<br>• QT prolongation<br>• Thrombocytopenia | More Frequent:<br>• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>Less Frequent:<br>• CNS effects (dizziness, drowsiness, headache)<br>• Alopecia | Can be given orally without regard to meals.<br>Shake suspension well before dosing.<br>Requires dose adjustment in patients with impaired renal function.<br>IV administration should be administered over 1–2 hours at a rate ≤200 mg/hour.<br>Daily dose is the same for oral and IV administration.<br>Multiple potential drug interactions<br>Monitor periodic LFTs, renal function, and CBC. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 10 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Flucytosine** (Ancobon) | Capsules:<br>• 250 mg<br>• 500 mg<br>Oral Liquid:<br>• Extempo-raneous preparation | More Frequent:<br>• Bone marrow suppression (especially leukopenia and thrombocytopenia)<br>Less Frequent:<br>• Hepatotoxicity<br>• Renal toxicity (including crystalluria)<br>Rare:<br>• Cardiac toxicity (ventricular dysfunction, myocardial toxicity, cardiac arrest)<br>• CNS symptoms (hallucinations, seizures, peripheral neuropathy)<br>• Anaphylaxis<br>• Hearing loss | • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>• Elevated liver transaminases<br>• Skin rash<br>Rare:<br>• CNS symptoms (headache, drowsiness, confusion, vertigo)<br>• Crystalluria | Monitor serum concentrations and adjust dose to maintain therapeutic levels and minimize risk of bone marrow suppression.<br>Requires dose adjustment in patients with impaired renal function; use with extreme caution.<br>Fatal aplastic anemia and agranulocytosis have been rarely reported.<br>Oral preparations should be administered with food over a 15-minute period to minimize GI side effects<br>Monitor CBC, LFTs, renal function, and electrolytes. |
| **Foscarnet** (Foscavir) | IV | More Frequent:<br>• Nephrotoxicity<br>• Serum electrolyte abnormalities (hypocalcaemia, hypophosphatemia, hypomagnesemia, hypokalemia)<br>Less Frequent:<br>• Hematologic toxicity (anemia, granulocytopenia)<br>• Neurotoxicity (muscle twitching, tremor, seizures, tingling around mouth)<br>• Cardiac abnormalities secondary to electrolyte changes<br>• Phlebitis (at site of injection)<br>Rare:<br>• Sores or ulcers mouth or throat | Frequent:<br>• GI disturbances (abdominal pain, anorexia, nausea, vomiting)<br>• Anxiety, confusion, dizziness, headache<br>• Fever | Requires dose adjustment in patients with impaired renal function.<br>Use adequate hydration to decrease nephrotoxicity. Avoid concomitant use of other drugs with nephrotoxicity.<br>Monitor serum electrolytes, renal function, and CBC.<br>Consider monitoring serum concentrations (TDM)<br>IV solution of 24 mg/mL can be administered via central line but must be diluted to a final concentration not to exceed 12 mg/mL if given via peripheral line.<br>Must be administered at a constant rate by infusion pump over ≥2 hours (or no faster than 1 mg/kg/minute). |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 11 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Ganciclovir** (Cytovene) | Capsules:<br>• 250 mg<br>• 500 mg<br>IV | More Frequent:<br>• Granulocytopenia<br>• Thrombocytopenia<br>Less Frequent:<br>• Anemia<br>• CNS effects (confusion, headache)<br>• Hypersensitivity (fever, rash)<br>• Elevated transaminase enzymes<br>• Increase in creatinine, BUN<br>• Phlebitis (at injection sites)<br>Rare:<br>• Retinal detachment<br>• Seizures<br>• Psychosis<br>• Cardiac (hypertension, chest pain) | • GI disturbances (abdominal pain, anorexia, nausea, vomiting)<br>• Rash | Requires dose adjustment in patients with renal impairment.<br>Avoid other nephrotoxic drugs.<br>IV infusion over at least 1 hour. In-line filter required.<br>Maintain good hydration.<br>Undiluted IV solution is alkaline (pH 11); use caution in handling and preparing solutions and avoid contact with skin and mucus membranes.<br>Administer oral doses with food to increase absorption. Do not open or crush capsules.<br>Monitor CBC, LFTs, renal function; conduct ophthalmologic examinations. |
| **Interferon-alfa-2B** (IFN-α-2B; Intron) | Parenteral (SQ or IV use) | More Frequent:<br>• Hematologic toxicity (leukopenia, thrombocytopenia)<br>• Neurotoxicity (confusion, depression, insomnia, anxiety)<br>• Injection erythema<br>Less Frequent:<br>• Cardiovascular effects (chest pain, hypertension, arrhythmias, hypotension)<br>• Hypoesthesia/paresthesia<br>Rare:<br>• Abnormality or loss of vision<br>• Allergic reaction (rash, hives)<br>• Hypothyroidism<br>• Development of antinuclear antibodies | More Frequent:<br>• Flu-like syndrome (myalgia, arthralgia, fever, chills, headache, back pain, malaise, fatigue)<br>• GI disturbances (abdominal pain, anorexia, nausea, vomiting, diarrhea, dyspepsia)<br>• Pharyngitis, dry mouth<br>Less Frequent:<br>• Alopecia<br>• Epistaxis<br>• Elevated serum transaminases, serum creatinine and BUN, glucose, triglycerides | Severe adverse effects less common in children than adults.<br>Toxicity dose-related, with significant reduction over the first 4 months of therapy.<br>For non-life-threatening reactions, reduce dose or temporarily discontinue drug and restart at low doses with stepwise increases.<br>If patients have visual complaints, an ophthalmologic exam should be performed to detect possible retinal hemorrhage or retinal artery or vein obstruction.<br>Should not be used in children with decompensated hepatic disease, significant cytopenia, autoimmune disease, or significant pre-existing renal or cardiac disease.<br>If symptoms of hepatic decompensation occur |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 12 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Interferon-alfa-2B** (IFN-α-2B; Intron), continued | | | | (ascites, coagulopathy, jaundice), IFN-α-2B should be discontinued.<br>Reconstituted solution stable for 24 hours when refrigerated.<br>Monitor CBC, renal function, LFTs, thyroid function, and glucose. |
| **Isoniazid** (Nydrazid) | Oral Syrup:<br>• 10 mg/mL<br>Tablets:<br>• 100 mg<br>• 300 mg<br>IM | More Frequent:<br>• Hepatitis prodromal syndrome (anorexia, weakness, vomiting)<br>• Hepatitis<br>• Peripheral neuritis<br>Rare:<br>• Blood dyscrasias<br>• Hypersensitivity (fever, rash, joint pain)<br>• Neurotoxicity (includes seizure)<br>• Optic neuritis | • GI disturbances (abdominal pain, nausea, vomiting, diarrhea)<br>• Elevated liver transaminases<br>• Pyridoxine deficiency | Take with food to minimize gastric irritation.<br>Take ≥1 hour before aluminum-containing antacids.<br>Hepatitis less common in children.<br>Use with caution in patients with hepatic function impairment, severe renal failure, or history of seizures.<br>Pyridoxine supplementation should be provided for all HIV-infected children.<br>Monitor LFTs and periodic ophthalmologic examinations. |
| **Itraconazole** (Sporanox) | Oral Solution:<br>• 10 mg/mL<br>Capsules:<br>• 100 mg<br>IV | Less frequent:<br>• Hypersensitivity (fever, chills, skin rash)<br>• Hypokalemia (can be associated with cardiac arrhythmias)<br>Rare:<br>• Hepatotoxicity<br>• Hematologic abnormalities (thrombocytopenia, leukopenia) | More Frequent:<br>• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>Less Frequent:<br>• CNS effects (dizziness, drowsiness, headache)<br>• Rash | Oral Solution:<br>• Give on an empty stomach because gastric acid increases absorption.<br>Capsules:<br>• Administer after a full meal to increase absorption.<br>Itraconazole oral solution has 60% greater bioavailability compared with capsules, and the oral solution and capsules should not be used interchangeably.<br>IV infusion over 1 hour.<br>Multiple potential drug interactions<br>Monitor LFTs and potassium levels.<br>Monitor serum concentrations (TDM) in severe infections. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 13 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Kanamycin** | IV<br>IM | More Frequent:<br>• Nephrotoxicity<br>• Neurotoxicity (including muscle twitching, seizures)<br>• Ototoxicity, both auditory and vestibular<br>Less Frequent:<br>• Hypersensitivity (skin rash, redness or swelling)<br>Rare:<br>• Neuromuscular blockade | N/A | Must be infused over 30 to 60 minutes to avoid neuromuscular blockade.<br>Requires dose adjustment in patients with impaired renal function.<br>Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy.<br>Monitor serum concentrations (TDM).<br>Monitor renal function; conduct, hearing exams for patients receiving prolonged therapy. |
| **Ketoconazole** (Nizoral) | Tablets:<br>• 200 mg<br>Topical:<br>• Shampoo<br>• Cream<br>• Gel<br>• Foam<br>Suspension:<br>• Extempo-raneous preparation | Less Frequent:<br>• Hypersensitivity (fever, chills, skin rash)<br>Rare:<br>• Hepatotoxicity (including hepatic failure) | Frequent:<br>• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>Less Frequent:<br>• CNS effects (dizziness, drowsiness, headache)<br>Rare:<br>• Gynecomastia<br>• Impotence<br>• Menstrual irregularities<br>• Photophobia | Adverse GI effects occur less often when administered with food.<br>Drugs that decrease gastric acidity or sucralfate should be administered ≥2 hours after ketoconazole.<br>Disulfiram-like reactions have occurred in patients ingesting alcohol.<br>Hepatotoxicity is an idiosyncratic reaction, usually reversible when stopping the drug, but rare fatalities can occur any time during therapy; more common in females and adults >40 years, but cases reported in children.<br>High-dose ketoconazole suppresses corticosteroid secretion, lowers serum testosterone concentration (reversible).<br>Multiple potential drug interactions.<br>Monitor LFTs. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 14 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Mefloquine**<br>(Lariam) | Tablets:<br>• 250 mg | More Frequent:<br>• CNS (psychosis, depression, hallucinations, paranoia, seizures)<br>Rare:<br>• Blood dyscrasias<br>• Cholestasis, elevated bilirubin | • Rash<br>• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>• CNS (dizziness, vivid dreams, insomnia)<br>• Tinnitus, blurred vision | Side effects less prominent in children.<br>Administer with food and plenty of water.<br>Tablets can be crushed and added to food; bitter tasting so administer with foods that can mask the taste<br>Monitor LFTs. |
| **Nitazoxanide**<br>(Alinia) | Oral Suspension:<br>• 20 mg/mL<br>Tablets:<br>• 500 mg | N/A | More Frequent:<br>• GI disturbances (abdominal pain, nausea, vomiting)<br>• Headache<br>Rare:<br>• Scleral icterus<br>• Rash | Should be given with food.<br>Shake suspension well prior to dosing. |
| **P-Aminosalicyclic Acid**<br>(Paser) | Delayed Release Granules:<br>• 4 g per packet | Rare:<br>• Hypersensitivity (fever, skin rash, exfoliative dermatitis, mono-like or lymphoma-like syndrome, jaundice, hepatitis, pericarditis, vasculitis, hematologic abnormalities including hemolytic anemia, hypoglycemia, optic neuritis, encephalopathy, reduction in prothrombin)<br>• Crystalluria<br>• Hemolytic anemia | • GI disturbances (abdominal pain, nausea, vomiting, diarrhea) | Should not be administered to patients with severe renal disease.<br>Drug should be discontinued at first sign of hypersensitivity reaction (rash, fever, and GI symptoms typically precede jaundice).<br>Vitamin B12 therapy should be considered in patients receiving for >1 month.<br>Administer granules by sprinkling on acidic foods such as applesauce or yogurt or a fruit drink like tomato or orange juice.<br>Maintain urine at neutral or alkaline pH to avoid crystalluria.<br>The granule soft "skeleton" may be seen in the stool.<br>Monitor CBC and LFTs. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 15 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Pegylated Interferon Alfa-2A** (Pegasys) | Injection:<br>• Vials and prefilled syringes | More Frequent:<br>• Hematologic toxicity (leukopenia, thrombocytopenia)<br>• Neurotoxicity (confusion, depression, insomnia, anxiety)<br>• Injection erythema<br>Less Frequent:<br>• Cardiovascular effects (chest pain, hypertension, arrhythmias, hypotension)<br>• Hypoesthesia/paresthesia<br>Rare:<br>• Vision abnormalities or loss of vision<br>• Allergic reaction (rash, hives)<br>• Hypothyroidism<br>• Development of antinuclear antibodies | More Frequent:<br>• Flu-like syndrome (myalgia, arthralgia, fever, chills, headache, back pain, malaise, fatigue)<br>• GI disturbances (abdominal pain, anorexia, nausea, vomiting, diarrhea, dyspepsia)<br>• Pharyngitis, dry mouth<br>Less Frequent:<br>• Alopecia<br>• Epistaxis<br>• Elevated serum transaminases, serum creatinine and BUN, glucose, triglycerides | Toxicity dose-related. Dose modifications based on type and degree of toxicity.<br>For non-life threatening reactions, reduce dose or temporarily discontinue drug and restart at low doses with stepwise increases.<br>If patients have visual complaints, an ophthalmologic exam should be performed to detect possible retinal hemorrhage or retinal artery or vein obstruction.<br>Should not be used in children with decompensated hepatic disease, significant cytopenia, autoimmune disease, or significant pre-existing renal or cardiac disease.<br>If symptoms of hepatic decompensation occur (ascites, coagulopathy, jaundice),Peg- IFN-α-2A should be discontinued.<br>Monitor CBC, renal function, LFTs, thyroid function, and glucose.<br>Store vials and syringes in refrigerator. Protect from light.<br>Administer SQ in abdomen or thigh. Rotate injection sites. |
| **Pegylated Interferon Alfa-2B** (Pegintron) | Injection:<br>• Vials and prefilled syringes | More Frequent:<br>• Hematologic toxicity (leukopenia, thrombocytopenia)<br>• Neurotoxicity (confusion, depression, insomnia, anxiety)<br>• Injection erythema<br>Less Frequent:<br>• Cardiovascular effects (chest pain, hypertension, arrhythmias, hypotension)<br>• Hypoesthesia/paresthesia | More Frequent:<br>• Flu-like syndrome (myalgia, arthralgia, fever, chills, headache, back pain, malaise, fatigue)<br>• GI disturbances (abdominal pain, anorexia, nausea, vomiting, diarrhea, dyspepsia)<br>• Pharyngitis, dry mouth<br>Less Frequent:<br>• Alopecia<br>• Epistaxis<br>• Elevated serum | Toxicity dose-related. Dose modifications based on type and degree of toxicity.<br>For non-life threatening reactions, reduce dose or temporarily discontinue drug and restart at low doses with stepwise increases.<br>If patients have visual complaints, an ophthalmologic exam should be performed to detect possible retinal hemorrhage or retinal artery or vein obstruction. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 16 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Pegylated Interferon Alfa-2B** (Pegintron), continued | | Rare:<br>• Abnormality or loss of vision<br>• Allergic reaction (rash, hives)<br>• Hypothyroidism<br>• Development of antinuclear antibodies | transaminases, serum creatinine and BUN, glucose, triglycerides | Should not be used in children with decompensated hepatic disease, significant cytopenia, autoimmune disease, or significant pre-existing renal or cardiac disease.<br>If symptoms of hepatic decompensation occur (ascites, coagulopathy, jaundice),Peg- IFN-α-2A should be discontinued.<br>Monitor CBC, renal function, LFTs, thyroid function, and glucose.<br>Store vials and syringes in refrigerator. Protect from light.<br>Administer SQ in abdomen or thigh. Rotate injection sites. |
| **Pentamidine** (Pentam) | IV<br>Aerosol | IV<br>*More Frequent:*<br>• Nephrotoxicity<br>• Hypoglycemia<br>• Hyperglycemia or diabetes mellitus<br>• Elevated liver transaminases<br>• Hypotension<br>• Leukopenia or neutropenia<br>• Thrombocytopenia<br>*Less Frequent:*<br>• Anemia<br>• Cardiac arrhythmias<br>• Hypersensitivity (skin rash, fever)<br>• Pancreatitis<br>• Phlebitis<br>• Sterile abscess (at site injection)<br>Aresol<br>*More Frequent:*<br>• Sneezing<br>• Cough | IV<br>*More Frequent:*<br>• GI disturbances (anorexia, nausea, vomiting, diarrhea)<br>*Less Frequent:*<br>• Unpleasant metallic taste<br>Aresol<br>*More Frequent:*<br>• Bronchospasm | Rapid infusion may result in precipitous hypotension; IV infusion should be administered over ≥1 hour (preferably 2 hours).<br>Cytolytic effect on pancreatic beta islet cells, leading to insulin release, can result in prolonged severe hypoglycemia (usually occurs after 5–7 days of therapy, but can also occur after the drug is discontinued); risk increased with higher dose, longer duration of therapy, and re-treatment within 3 months of prior treatment.<br>Hyperglycemia and diabetes mellitus can occur up to several months after drug discontinued.<br>Monitor LFTs, renal function, glucose, electrolytes, BP.<br>Inhalation:<br>• A special nebulizer is required for aerosol administration. Medical personnel should be trained in the proper administration of aerosolized pentamidine. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 17 of 22)

| Drug | Preparations | Major Toxicities[a]: Indicating Need for Medical Attention | Major Toxicities[a]: Indicating Need for Medical Attention if Persistent or Bothersome | Special Instructions |
|---|---|---|---|---|
| **Posaconazole** (Noxafil) | Oral Solution:<br>• 40 mg/mL | Less frequent:<br>• Hypersensitivity (fever, chills, skin rash)<br>• Anaphylactoid reaction with IV infusion<br>Rare:<br>• Hepatotoxicity (including hepatic failure)<br>• Exfoliative skin disorders (including SJS)<br>• Renal dysfunction<br>• Cardiac arrhythmias (QT interval prolongation, torsades de pointes, hypertension)<br>• Hemolytic uremic syndrome<br>• Pulmonary embolism<br>• Neutropenia | • Bone marrow suppression<br>• Muscular pain<br>• CNS: headache, dizziness, fatigue<br>• Elevated serum transaminases | Must be given with meals. Adequate absorption is dependent on food for efficacy.<br>Monitor LFTs, renal function and electrolytes.<br>Monitor serum drug concentrations (TDM).<br>Shake suspension prior to dosing. |
| **Primaquine** | Tablets:<br>• 15 mg (base) = 26.3 mg primaquine phosphate | More Frequent:<br>• Hemolytic anemia (with G6PD deficiency)<br>Less Frequent:<br>• Methemoglobinemia<br>Rare:<br>• Leukopenia | • GI disturbances (nausea, vomiting) | Take with meals or antacids to minimize gastric irritation.<br>Store in a light-resistant container.<br>Bitter taste.<br>Monitor CBC. |
| **Pyrazinamide** | Tablets:<br>• 500 mg<br>Oral Suspension:<br>• Extempo-raneous preparation | More Frequent:<br>• Arthralgia<br>Less Frequent:<br>• Hepatotoxicity (dose-related)<br>Rare:<br>• Acute gouty arthritis secondary to hyperuricemia<br>• Thrombocytopenia, anemia<br>• Interstitial nephritis<br>• Porphyria | • Skin rash, pruritus<br>• Photosensitivity<br>• Malaise<br>• GI disturbances (nausea, vomiting)<br>• Arthralgia<br>• Hyperuricemia | Avoid in patients with severe hepatic impairment.<br>Reduce dose in patients with renal or hepatic impairment.<br>Monitor LFTs and uric acid. |
| **Pyrimethamine** (Daraprim) | Tablet:<br>• 25 mg<br>Oral Suspension:<br>• Extempo-raneous preparation | Less Frequent:<br>• Neutropenia<br>• Thrombocytopenia<br>• Megaloblastic anemia<br>Rare:<br>• SJS<br>• Seizure | • Skin rash<br>• Photosensitivity<br>• Dry mouth<br>• GI disturbances (nausea, vomiting)<br>• CNS (depression, insomnia | To prevent hematologic toxicity, administer with leucovorin.<br>Monitor CBC. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 18 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Quinidine** | IV | Serious:<br>• Cardiac arrhythmias<br>• QT interval prolongation<br>• Hypoglycemia<br>• Hemolytic anemia (with G6PD deficiency)<br>• Hepatotoxicity | Very Frequent:<br>• Cinchonism—syndrome of tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium; dose dependent | EKG monitoring is standard of care.<br>Do not give by bolus infusion.<br>If EKG changes observed, slow infusion rate.<br>Monitor CBC and LFTs. |
| **Ribavirin**<br>Virazole<br>*Powder for solution for nebulization*<br>Rebetol<br>*Oral capsules and oral solution*<br>Copegus, Ribasphere, Ribapak<br>*Oral tablets and capsules* | Powder for Solution for Nebulization:<br>• Reconstituted product contains 20 mg/mL<br>Oral Solution:<br>• 40 mg/mL<br>Capsules:<br>• 200 mg<br>Tablets:<br>• 200 mg<br>• 400 mg<br>• 600 mg | • Hemolytic anemia (with associated potential for increase in unconjugated bilirubin and uric acid)<br>Less Frequent:<br>• Neutropenia, thrombocytopenia, anemia<br>• Pancreatitis | • CNS effects (fatigue, headache, insomnia, depression)<br>• GI disturbances (abdominal pain, nausea, vomiting)<br>• Skin rash<br>• Myalgia, arthralgia, weakness | Should not be used in patients with severe renal impairment.<br>Should not be used as monotherapy for treatment of hepatitis C, but used in combination with IFN-α.<br>Intracellular phosphorylation of pyrimidine nucleoside analogues (zidovudine, stavudine, zalcitabine) decreased by ribavirin, may have antagonism; use with caution.<br>Enhances phosphorylation of didanosine; use with caution because of increased risk of pancreatitis/mitochondrial toxicity.<br>Oral solution contains propylene glycol.<br>Teratogenic/embryocidal. Contraindicated in pregnant women and their male partners. Avoid pregnancy for additional 6 months after treatment.<br>Monitor CBC, renal function, LFTs, and thyroid function. Perform pregnancy tests regularly while on therapy. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 19 of 22)

| Drug | Preparations | Major Toxicities[a] Indicating Need for Medical Attention | Major Toxicities[a] Indicating Need for Medical Attention if Persistent or Bothersome | Special Instructions |
|---|---|---|---|---|
| **Rifabutin** (Mycobutin) | Capsules:<br>• 150 mg<br>Oral Suspension:<br>• Extempo-raneous preparation | More Frequent:<br>• Allergic reaction (rash, pruritus)<br>• Neutropenia<br>Less Frequent:<br>• Asthenia<br>Rare:<br>• Arthralgia, myalgia<br>• Change in taste<br>• Pseudojaundice<br>• Thrombocytopenia<br>• Uveitis | • Headache<br>• Insomnia<br>• Rash, staining of skin<br>• GI disturbances (abdominal pain, diarrhea, nausea, vomiting, anorexia) | Preferably take on empty stomach, but may be administered with food in patients with GI intolerance.<br>The contents of capsules may be mixed with applesauce if patient is unable to swallow capsule.<br>May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses).<br>Uveitis seen with high-dose rifabutin (i.e., adults >300 mg/day), especially when combined with clarithromycin.<br>Multiple potential drug interactions<br>Use with caution in patients with renal or hepatic impairment.<br>Monitor CBC, LFTs; conduct ophthalmologic examinations.<br>Reduce dose in patients with renal impairment. |
| **Rifampin** (Rifadin) | Oral Suspension:<br>• Extempo-raneous preparation<br>Capsules:<br>• 150 mg<br>• 300 mg<br>IV | Less Frequent:<br>• Flu-like syndrome<br>Rare:<br>• Blood dyscrasias<br>• Hepatitis prodromal syndrome (anorexia, nausea, vomiting, weakness)<br>• Hepatitis<br>• Interstitial nephritis<br>• Exfoliative skin disorders (including SJS) | • GI disturbances (abdominal pain, diarrhea)<br>• CNS effects (fatigue, headache, insomnia, depression)<br>• Rash<br>• Discoloration of body fluids<br>• Elevated serum transaminases<br>• Visual changes | Preferably take on empty stomach, but can be administered with food in patients with GI intolerance; take with full glass of water.<br>Suspension formulation stable for 30 days. Shake well prior to dosing.<br>May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses).<br>Multiple potential drug interactions<br>Use with caution in patients with hepatic impairment.<br>Administer IV by slow infusion. Extravasation may cause local irritation and inflammation.<br>Monitor CBC and LFTs. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 20 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Streptomycin** | IM | More Frequent:<br>• Nephrotoxicity<br>• Neurotoxicity (including muscle twitching, seizures)<br>• Peripheral neuritis<br>• Ototoxicity, both auditory and vestibular<br>Less Frequent:<br>• Hypersensitivity (skin rash, redness, or swelling)<br>• Optic neuritis<br>• Bone marrow suppression<br>Rare:<br>• Neuromuscular blockade | • CNS effects (headache, ataxia, dizziness ) | Usual route of administration is deep IM injection into large muscle mass.<br>For patients who cannot tolerate IM injections, dilute to 12–15 mg in 100 mL of 0.9% sodium chloride; must be infused over 30 to 60 minutes to avoid neuromuscular blockade.<br>Requires dose adjustment in patients with impaired renal function.<br>Monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy.<br>Monitor serum concentrations (TDM). |
| **Sulfadiazine** | Tablet:<br>• 500 mg<br>Oral Suspension:<br>• Extempo-raneous preparation | Rare:<br>• Crystalluria, renal failure<br>• Bone marrow suppression/ blood dyscrasias<br>• Severe hypersensitivity syndrome<br>• Hemolytic anemia (with G6PD deficiency) | • GI disturbances (abdominal pain, diarrhea, nausea)<br>• CNS effects (headache, dizziness)<br>• Rash<br>• Photosensitivity | Ensure adequate fluid intake to avoid crystalluria.<br>Monitor CBC, renal function, and urinalysis.<br>Monitor serum concentrations (TDM) if serious infection. |
| **Trimethoprim-Sulfameth-oxazole** (TMP-SMX) (Bactrim, Septra) | Oral Suspension:<br>• TMP 8 mg/mL and SMX 40 mg/mL<br>Tablets<br>*Single Strength:*<br>• TMP 80 mg and SMX 400 mg<br>*Double Strength:*<br>• TMP 160 mg and SMX 800 mg<br>IV | More Frequent:<br>• Skin rash<br>Less Frequent:<br>• Hypersensitivity reactions (skin rash, fever)<br>• Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia)<br>Rare:<br>• Exfoliative skin disorders (including SJS)<br>• Hemolytic anemia (with G6PD deficiency)<br>• Methemoglobinemia<br>• Renal toxicity (crystalluria, nephritis, tubular necrosis)<br>• CNS toxicity (aseptic meningitis)<br>• Pseudomembranous colitis<br>• Cholestatic hepatitis<br>• Thyroid function disturbance | • GI disturbances (anorexia, nausea, vomiting, diarrhea)<br>• Photosensitivity<br>• Rash | Requires dose adjustment in patients with impaired renal function.<br>Maintain adequate fluid intake to prevent crystalluria and stone formation (take with full glass of water).<br>Potential for photosensitivity skin reaction with sun exposure.<br>IV infusion over 60 to 90 minutes<br>Monitor CBC, renal function. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 21 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | Indicating Need for Medical Attention | Indicating Need for Medical Attention if Persistent or Bothersome | |
| **Valacyclovir** (Valtrex) | <u>Tablets</u>:<br>• 500 mg<br>• 1 g<br>**Note:** An oral suspension formulation 50 mg/mL can be prepared in Ora-Sweet or Syrpalta syrups) | <u>Rare</u>:<br>• Renal failure<br>• Bone marrow suppression<br>• Thrombotic microangiopathy/hemolytic uremic syndrome<br>• CNS (psychosis, seizures, delirium) | <u>More Frequent</u>:<br>• Headache, nausea<br><u>Less Frequent</u>:<br>• Arthralagia<br>• Dizziness, fatigue<br>• GI disturbances (diarrhea or constipation, anorexia, abdominal pain, vomiting)<br>• Dysmenorrhea | Thrombotic thrombocytopenia purpura/hemolytic uremic syndrome has been reported in HIV-infected adults with advanced disease receiving high (i.e., 8 g/day) but not low doses.<br>Monitor CBC and renal function. |
| **Valganciclovir** (Valcyte) | <u>Tablets</u>:<br>• 450 mg<br><u>Oral Solution</u>:<br>• 50 mg/mL | <u>More Frequent</u>:<br>• Granulocytopenia<br>• Thrombocytopenia<br><u>Less Frequent</u>:<br>• Anemia<br>• CNS effects (seizures, psychosis, hallucinations<br>• Hypersensitivity (fever, rash)<br>• Elevated transaminase enzymes<br>• Increase in creatinine, BUN<br>• Retinal detachment | • GI disturbances (abdominal pain, anorexia, nausea, vomiting)<br>• CNS effects (headache, insomnia) | Requires dose adjustment in patients with renal impairment.<br>Avoid other nephrotoxic drugs.<br>Tablets should not be broken or crushed.<br>Monitor CBC and renal function.<br>Potentially teratogenic and carcinogenic. |

**Table 4. Common Drugs Used for Treatment of Opportunistic Infections in HIV-Infected Children: Preparations and Major Toxicities** (page 22 of 22)

| Drug | Preparations | Major Toxicities[a] | | Special Instructions |
|---|---|---|---|---|
| | | **Indicating Need for Medical Attention** | **Indicating Need for Medical Attention if Persistent or Bothersome** | |
| **Voriconazole** (VFEND) | Tablet:<br>• 50 mg<br>• 200 mg<br>Oral Suspension:<br>• 40 mg/mL<br>IV | Less Frequent:<br>• Hypersensitivity (fever, chills, skin rash)<br>• Anaphylactoid reaction with IV infusion<br>Rare:<br>• Hepatotoxicity (including hepatic failure)<br>• Exfoliative skin disorders (including SJS)<br>• Renal dysfunction<br>• Cardiac arrhythmias<br>• Pancreatitis<br>• QT prolongation<br>• Electrolyte abnormalities<br>• Optic neuritis, papilledema | More Frequent:<br>• Visual changes, dose-related (photophobia, blurry vision)<br>• CNS effects (dizziness, drowsiness, headache)<br>• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting)<br>• Photosensitivity<br>Rare:<br>• Gynecomastia<br>• Elevated serum transaminases | Oral tablets should be taken 1 hour before or after a meal.<br>Shake oral suspension well prior to dosing.<br>Maximum IV infusion rate 3 mg/kg/hour over 1 to 2 hours.<br>Oral administration to patients with impaired renal function if possible (accumulation of IV vehicle occurs in patients with renal insufficiency)<br>Dose adjustment needed if hepatic insufficiency.<br>Visual disturbances common (>30%) but transient and reversible when drug is discontinued.<br>Multiple potential drug interactions<br>Monitor renal function, electrolytes, and LFTs<br>Consider monitoring serum concentrations (TDM). |

[a] The toxicities listed in the table have been selected based on their potential clinical significance and are not inclusive of all side effects reported for a particular drug.

**Key to Acronyms:** ARV = antiretroviral; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; Cr = creatinine; CrCl = creatinine clearance; EKG = electrocardiogram; G6PD = Glucose-6-phosphate dehydrogenase; GI = gastrointestinal; IFN- = interferon alfa; IM = intramuscular; IND = investigational new drug; IV = intravenous; LFT = liver function test; SJS = Stevens-Johnson Syndrome; SMX = sulfamethoxazole; SQ = subcutaneous; TDM = therapeutic drug monitoring; TMP = trimethoprim

# Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

There is the potential for significant drug interactions and overlapping toxicities in patients receiving medications for treatment or prevention of opportunistic infections (OIs). These patients often are receiving other medications, including antiretrovirals that interfere with metabolism or elimination of OI medications. In particular, protease inhibitors and non-nucleoside reverse transcriptase inhibitors affect the CYP450 or other transporter systems and may be associated with clinically significant drug interactions. The integrase inhibitor raltegravir is metabolized by UGT1A1 and may be a suitable option when trying to minimize interactions with other drug classes.

Table 5 provides clinicians with information regarding known or suspected drug interactions between drugs commonly used for treatment or prevention of HIV-associated OIs and treatment of HIV infection. Drug interaction information is generally obtained from studies involving healthy adult volunteers. Some pharmacokinetic (PK) data are available from studies involving HIV-infected adults, whereas data in children are extremely limited. New information continues to become available and it is important to carefully review a patient's current medications, including prescription and over-the-counter medications. It is difficult to predict the interaction potential when three or more drugs with similar metabolic pathways are co-administered and there is substantial inter-patient variability in the magnitude of these interactions. When possible, alternative agents with less drug interaction potential or use of therapeutic drug monitoring should be considered.

**Table 5 contains only a partial listing of drug interactions for drugs used to treat or prevent OIs.** The links below are excellent resources for investigating the potential for drug interactions. These tools include more comprehensive information and provide up-to-date information as new PK data become available.

http://www.hiv-druginteractions.org/

http://tdm.pharm.buffalo.edu/home/di_search/

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions/

http://www.drugs.com/drug_interactions.html

http://hivinsite.ucsf.edu/InSite?page=ar-00-02

http://www.nynjaetc.org/clinical_support.html

http://www.clinicaloptions.com/inPractice.aspx

http://epocrates.com

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 1 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| *** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).** | | |
| **Acyclovir** (Zovirax) | <u>Overlapping Toxicities</u>:<br>• Nephrotoxic drugs | Monitor for toxicities of these drugs. |
| | <u>Increased Concentrations (Both Drugs) and Overlapping Toxicities</u>:<br>• Antivirals: valacyclovir, valganciclovir, ganciclovir, cidofovir<br>• ARVs: tenofovir | Monitor for toxicities of these drugs. |
| **Albendazole** | <u>Increases Albendazole Concentrations</u>:<br>• Anthelmintic drugs: praziquantel | Caution advised. |
| **Amikacin** | <u>Overlapping Toxicities</u>:<br>• Anti-tuberculosis drugs (injectable): streptomycin, kanamycin<br>• Nephrotoxic or ototoxic drugs<br>• Antimycobacterial drugs: capreomycin<br>• Antivirals: cidofovir | Caution advised. Avoid combination of amikacin and cidofovir. |
| **Amphotericin B**<br>Amphotericin B Lipid Complex (Abelcet)<br>Amphotericin B Liposome (Ambisome) | <u>Overlapping Toxicities</u>:<br>• Bone marrow suppressant drugs: corticosteroids<br>• Nephrotoxic drugs<br>• Neuromuscular blocking drugs | Caution advised. |
| **Atovaquone** | <u>Decreases Atovaquone Concentrations</u>:<br>• Antimycobacterial drugs: rifampin, rifabutin<br>• ARVs: lopinavir/ritonavir, atazanavir/ritonavir<br>• Antibiotics: doxycycline | Co-administration of atovaquone and rifampin should be avoided. |
| **Azithromycin** | <u>Overlapping Toxicities</u>:<br>• Artemether/lumefantrine, chloroquine, quinine | Caution advised. Increased risk of QT prolongation. |
| **Boceprevir** | Please see Adult OI guidelines for information about drug interactions, including warnings about interactions between boceprevir and HIV protease inhibitors. | |
| **Capreomycin** | <u>Overlapping Toxicities</u>:<br>• Nephrotoxic or ototoxic drugs<br>• Neuromuscular blocking drugs<br>• Antibacterial drugs: aminoglycosides (parenteral) | Caution advised. |
| **Caspofungin** | <u>Decreases Caspofungin Concentrations</u>:<br>• Anticonvulsant drugs: phenytoin<br>• Antimycobacterial drugs: rifampin<br>• ARV drugs: efavirenz, nevirapine | Increase in dose of caspofungin is recommended when co-administered with CYP450 inducers. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 2 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Cidofovir** | Overlapping Toxicities:<br>• Antibacterial drugs: aminoglycosides<br>• Antiviral drugs: foscarnet<br>• Nephrotoxic drugs | Monitor for toxicities of these drugs. |
| **Ciprofloxacin** | Decreases Ciprofloxacin Absorption:<br>• ARV drugs: didanosine<br>• Minerals: ferrous sulfate, zinc<br>• Gastrointestinal drugs: antacids, sucralfate, magnesium-containing laxatives | Give oral ciprofloxacin 2 hours before or 6 hours after drugs that may interfere with absorption. |
| | Overlapping Toxicities:<br>• Artemether/lumefantrine, clarithromycin, quinine | Caution advised. |
| **Clarithromycin** | Increases Clarithromycin Concentrations:<br>• ARV drugs: atazanavir/ritonavir, lopinavir/ritonavir<br>• Antifungals: itraconazole (itraconazole concentrations also increased) | Caution advised. Concern for QTc prolongation. Decrease clarithromycin dose or consider switching to azithromycin, which has less potential for drug interactions. |
| | Increases Concentration of Other Medications:<br>• ARV drugs: etravirine | Consider alternative agent. |
| | Decreases Clarithromycin Concentrations:<br>• ARV drugs: efavirenz, etravirine, nevirapine<br>• Antimycobacterial drugs: rifampin, rifabutin (rifabutin concentrations also increased) | Consider switching to azithromycin, which has less potential for drug interaction.<br>For concomitant use of rifabutin and clarithromycin, consider decreasing dose of rifabutin or switching to azithromycin. |
| **Clindamycin** | Decreases Clindamycin Antibacterial Efficacy:<br>• Antibacterial drugs: chloramphenicol, erythromycins | Avoid concomitant use. |
| **Cycloserine** | Overlapping Toxicities:<br>• Antimycobacterial drugs: ethionamide, isoniazid | Caution advised. |
| **Dapsone** | Decreases Dapsone Concentrations:<br>• Antimycobacterial drugs: rifampin | Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin. |
| | Decreases Dapsone Absorption:<br>• ARV drugs: didanosine suspension<br>• Gastrointestinal drugs: antacids | For co-administration with antacids or didanosine suspension, give dapsone 1 hour before or 4 hours after the other medication. |
| | Overlapping Toxicities:<br>• Bone marrow suppressant drugs or drugs associated with hemolysis | Caution advised. |
| **Doxycycline** | Decreases Doxycycline Concentrations:<br>• Anticonvulsant drugs: phenytoin, carbamazepine<br>• Antimycobacterial drugs: rifampin | Potential for decreased doxycycline efficacy. Monitor for therapeutic failure. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 3 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Erythromycin** | Increases Concentrations of Erythromycin and Co-Administered Medication:<br>• Antifungals: itraconazole | Monitor for toxicities of both drugs, potential for QT prolongation. |
| **Ethambutol** | Overlapping Toxicities:<br>• Neurotoxic drugs | Caution advised. |
| **Ethionamide** | Potential for Increased Toxicity Due to Overlapping Toxicity:<br>• Neurotoxic drugs<br>• Antimycobacterial drugs: cycloserine, isoniazid | Caution advised. |
| **Fluconazole** | Decreases Fluconazole Levels:<br>• Anticonvulsant drugs: phenytoin<br>• Antimycobacterial drugs: rifampin<br>• ARV drugs: rilpivirine | Monitor for efficacy. May need to increase fluconazole dose. |
| | Increases Concomitant Drug Concentrations:<br>• ARV drugs: saquinavir, tipranavir, nevirapine, and etravirine | May need to decrease dose of saquinavir. Avoid tipranivir with high doses of fluconazole (maximum fluconazole dose in adults: 200 mg). Caution advised with etravirine. |
| | • Antimycobacterial drugs: rifabutin | May need to decrease dose of rifabutin. |
| | • Statins: simvastatin, lovastatin, atorvastatin | Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy. |
| **Flucytosine** | Increases Flucytosine Concentrations:<br>• Nephrotoxic drugs | Caution advised. |
| **Foscarnet** | Overlapping Toxicities:<br>• Antiviral drugs: cidofovir<br>• Anti-pneumocystis drugs: pentamidine<br>• Nephrotoxic drugs | Monitor for toxicities of these drugs. |
| **Ganciclovir** | Increases Ganciclovir Concentrations :<br>• ARV drugs: tenofovir (concentrations also increased) | Monitor for toxicities of these drugs. |
| | Increases Concomitant Drug Concentrations:<br>• ARV drugs: didanosine, tenofovir | Caution advised. |
| | Overlapping Toxicities:<br>• Antibacterial drugs: imipenem-cilastatin<br>• ARV drugs: zidovudine<br>• Bone marrow suppressant drugs<br>• Nephrotoxic drugs | Caution advised. Increased risk of seizures with imipenem-cilastatin. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 4 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Interferon-Alfa** | Overlapping Toxicities:<br>• ARV drugs: zidovudine, lamivudine<br>• Bone marrow suppressant drugs | Co-administration of zidovudine and lamivudine should be avoided if possible. Caution advised with other bone marrow suppressant drugs. |
| **Isoniazid** | Decreases Isoniazid Concentrations:<br>• Corticosteroids: glucocorticoids (e.g., prednisolone) | Use with caution. |
| | Decreases Isoniazid Absorption:<br>• Gastrointestinal drugs: antacids | Caution advised. |
| | Increases Concomitant Drug Concentrations:<br>• Diazepam | Caution advised. |
| | Decreases Concomitant Drug Concentrations:<br>• Antifungal drugs: ketoconazole, itraconazole | Co-administration should be avoided, if possible. |
| | Overlapping Toxicities:<br>• Antimycobacterial drugs: rifampin, cycloserine, ethionamide<br>• Hepatotoxic drugs<br>• Neurotoxic drugs | Caution advised. |
| **Itraconazole** | Increases Itraconazole Concentration:<br>• Antibacterial: clarithromycin, erythromycin, ciprofloxacin<br>• ARVs: protease inhibitors | Monitor for toxicities. Monitor itraconazole concentration. Consider azithromycin instead of other macrolides. High doses of itraconazole are not recommended with PIs. |
| | Increases Concomitant Drug Concentrations:<br>• ARV drugs: etravirine, maraviroc, protease inhibitors | Caution advised. Monitor for toxicities. Decrease adult maraviroc dose to 150 mg twice daily. |
| | • Statins: lovastatin, simvastatin, atorvastatin | Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy. |
| | • Antibacterial: clarithromycin, erythromycin | Consider switching to azithromycin, which has less potential for drug interaction. |
| | • Sedatives/hypnotics: midazolam, alprazolam, diazepam | Co-administration of midazolam and alprazolam should be avoided. Co-administration of diazepam should be avoided, if possible. |
| | • Cardiac: quinidine | Co-administration of quinidine should be avoided. QT prolongation. |
| | Decreases Itraconazole Concentrations:<br>• ARV drugs: efavirenz, etravirine, nevirapine, rilpivirine | Monitor itraconazole concentration. Co-administration of efavirenz should be avoided if possible. |
| | • Anticonvulsant drugs: carbamazepine, (fos)phenytoin | Monitor itraconazole concentration. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 5 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Itraconazole,** continued | • Antimycobacterial drugs: rifampin, rifabutin, rifapentine, isoniazid | Co-administration with rifampin should be avoided. Co-administration with rifabutin should be avoided, if possible. Monitor for toxicities. Monitor itraconazole concentration. |
| | Decreases Itraconazole Absorption:<br>• ARV drugs: didanosine<br>• Gastrointestinal drugs: antacids, anticholinergics/antispasmodics, histamine $H_2$-receptor antagonists, omeprazole, sucralfate | Monitor itraconazole concentration. |
| **Lumefantrine** | Increases Concomitant Drug Levels:<br>• ARV drugs: nevirapine | Monitor for nevirapine toxicity. |
| | Overlapping Toxicities:<br>• ARV drugs: protease inhibitors<br>• Antibacterial drugs: macrolides, fluoroquinolones<br>• Antifungal drugs: fluconazole, voriconazole<br>• Antimalarial drugs: quinine, quinidine<br>• Psychotropic drugs: quetiapine, tricyclic antidepressants | Co-administration with fluconazole or voriconazole should be avoided. For all other drugs, co-administration should be avoided, if possible; monitor for toxicities (QT prolongation). |
| **Mefloquine** | Decreases Mefloquine Concentrations:<br>• Antimalarial drugs: quinine<br>• Antimycobacterial: rifampin | Monitor for decreased mefloquine efficacy.<br>Co-administration of rifampin should be avoided, if possible; use rifabutin instead. |
| | Decreases Concomitant Drug Concentrations:<br>• ARV drugs: ritonavir, possibly other protease inhibitors | Monitor for virologic failure of protease inhibitor-containing ART regimen. |
| | Overlapping Toxicities:<br>• Anti-malarial drugs: quinine<br>• Other drugs that can cause prolonged QT | Avoid co-administration, if possible. Monitor for toxicities (EKG changes, cardiac arrest; also seizures with quinine). If co-administered with quinine, give mefloquine at least 12 hours after last dose of quinine. |
| **Nitazoxanide** | Increases Concomitant Drug Concentrations:<br>• Phenytoin | Potential for interaction with other medications that are highly protein bound. Use with caution as interaction will increase concentrations of concomitant medication. |
| **Paromomycin** | Overlapping Toxicities:<br>• Neuromuscular blocking drugs | Use with caution. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 6 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| *** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).** | | |
| **Pentamidine** | Overlapping Toxicities:<br>• Antiviral drugs: foscarnet | Co-administration should be avoided, if possible. Monitor for toxicities (hypocalcaemia, QT prolongation). |
| | • ARV drugs: protease inhibitors, didanosine | Co-administration should be avoided, if possible. Monitor for toxicities (QT prolongation with protease inhibitors; pancreatitis for didanosine). |
| | • Bone marrow suppressant drugs | Monitor for toxicities. |
| | • Nephrotoxic drugs | Monitor for toxicities. |
| | • Other drugs that can cause prolonged QT | Monitor for toxicities. Avoid co-administration, if possible. |
| **Posaconazole** | Decreases Posaconazole Drug Concentrations:<br>• ARV drugs: efavirenz, fosamprenavir, rilpivirine | Co-administration of fosamprenavir should be avoided. Co-administration of efavirenz should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly. |
| | • Anticonvulsant drugs: phenytoin | Co-administration should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly. |
| | • Antimycobacterial drugs: rifabutin, rifampin | Co-administration should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly. |
| | Increases Concomitant Drug Concentrations:<br>• ARV drugs: atazanavir, saquinavir, lopinavir, etravirine, and ritonavir | Co-administration should be avoided, if possible. Monitor for toxicities. Consider monitoring concentrations and adjust dose as necessary. |
| | • Antibacterial drugs: erythromycin, clarithromycin | Co-administration should be avoided. |
| | • Anticonvulsant drugs: phenytoin | Co-administration should be avoided. |
| | • Sedatives/hypnotics: midazolam, alprazolam, diazepam | Co-administration should be avoided, if possible. Monitor for toxicities. |
| | • Antimycobacterial drugs: rifabutin | Co-administration should be avoided. |
| | • Statins: simvastatin, lovastatin, atorvastatin | Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy. |
| | • Antimalarials: Quinidine, quinine, mefloquine, lumefantrine, halofantrine | Co-administration should be avoided. |
| | Decreases Concomitant Drug Concentrations:<br>• ARV drugs: fosamprenavir | Co-administration should be avoided. |
| | • Other drugs that can cause prolonged QT | Use with caution. Monitor for toxicities. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 7 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Proguanil** | Decreases Proguanil Concentrations:<br>• Atazanavir/ritonavir, lopinavir/ritonavir, efavirenz | Use with caution. |
| **Pyrazinamide** | Overlapping Toxicities:<br>• Antimycobacterial drugs: rifampin, ethionamide<br>• Hepatotoxic drugs | Use with caution. Monitor for hepatotoxicity. |
| **Quinidine** | Increases Quinidine Concentrations:<br>• Protease inhibitors | Co-administration of PIs should be avoided. Increased risk of arrhythmia. Co-administration may be necessary in presence of life-threatening, severe malaria and in the absence of other therapy, while artesunate is obtained from the CDC. |
| | • Itraconazole, posaconazole, voriconazole | Co-administration should be avoided. Increased risk of arrhythmia. |
| | Decreases Quinidine Concentrations:<br>• Etravirine | Use with caution. Monitor quinidine levels. |
| | Increases Concomitant Drug Concentrations:<br>• Tricyclic antidepressants | Co-administration should be avoided, if possible. Monitor for toxicities. |
| | Overlapping Toxicities:<br>• Other drugs that can prolong QT interval | Co-administration should be avoided, if possible. Monitor for toxicities (QT prolongation). |
| **Ribavirin** | Increases Concentrations Of Concomitant Drug:<br>• ARV drugs: didanosine | Co-administration should be avoided. Potential for increased risk of pancreatitis and mitochondrial toxicity. |
| | Decreases Concentrations of Concomitant Drug:<br>• Zidovudine, stavudine | Co-administration should be avoided, if possible. |
| | Overlapping Toxicities:<br>• Zidovudine, all NRTIs | Co-administration should be avoided, if possible. Monitor for toxicities (anemia for zidovudine; lactic acidosis for all NRTIs). |
| **Rifabutin** | Increases Rifabutin Concentrations:<br>• HIV protease inhibitors | Use with caution. Monitor for rifabutin toxicity. Reduce rifabutin dose if co-administered with PIs. |
| | • Fluconazole | Use with caution. Monitor for rifabutin toxicity. Consider rifabutin dose reduction. |
| | • Voriconazole, itraconazole, posaconazole | Co-administration should be avoided, if possible. If co-administered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy). |
| | • Clarithromycin | Co-administration should be avoided, if possible. Monitor for rifabutin toxicity. Consider rifabutin dose reduction or using azithromycin instead. |
| | Increases Concomitant Drug Concentrations:<br>• Didanosine | Use with caution. Monitor for didanosine toxicity. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 8 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Rifabutin,** continued | Decreases Rifabutin Concentrations:<br>• Efavirenz, etravirine | Use with caution. Higher rifabutin dose required when efavirenz co-administered. Consider TDM. |
| | Decreases Concomitant Drug Concentrations:<br>• ARV drugs: rilpivirine | Co-administration should be avoided. |
| | • ARV drugs: saquinavir, etravirine, maraviroc | Co-administration should be avoided, if possible. |
| | • Antibacterial drugs: dapsone, atovaquone | Use with caution. Monitor for dapsone treatment failure. |
| | • Antifungal drugs: azoles (except for fluconazole) | Co-administration should be avoided, if possible. If co-administered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy). |
| | • Contraceptives: oral | Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended. |
| **Rifampin** | Decreases Concomitant Drug Concentrations:<br>• Contraceptives: oral | Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended. |
| | • ARV drugs: PIs ± ritonavir, nevirapine, raltegravir, rilpivirine | Significantly decreases PI exposure; co-administration should be avoided. Nevirapine: use only if other options not available and close virologic and immunologic monitoring can be done; consider efavirenz instead. Raltegravir dose increase may be required. Rilpivirine co-administration should be avoided. |
| | • Antimicrobial: atovaquone, dapsone, clarithromycin, doxycycline | Co-administration of atovaquone and rifampin should be avoided. Consider switching clarithromycin to azithromycin, which has less potential for drug interaction. Dapsone and Doxycycline efficacy may be reduced. |
| | • Antifungal drugs: azoles, caspofungin | Increase in dose of caspofungin is recommended when co-administered with CYP450 inducers.<br>Azoles: Monitor for efficacy. May need to increase antifungal dose |
| | • Other: corticosteroids, methadone | Caution advised with corticosteroids (decreased efficacy).<br>Methadone: Monitor for efficacy and/or opiate withdrawal symptoms with methadone. |
| | Overlapping Toxicities:<br>• Bone marrow suppressant drugs<br>• Hepatotoxic drugs | Monitor for toxicities of these drugs. |
| **Streptomycin** | Potential for Increased Toxicity Due to Overlapping Toxicity:<br>• Nephrotoxic drugs<br>• Neuromuscular blocking drugs | Monitor for toxicities of these drugs. |

**Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections** (page 9 of 9)

| Drug Name | Overlapping Toxicities | Recommendation |
|---|---|---|
| * The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions). | | |
| **Telaprevir** | Please see Adult OI guidelines for information about drug interactions, including warnings about interactions between telaprevir and HIV protease inhibitors. Caution advised. | |
| **Trimethoprim-Sulfamethoxazole** | Overlapping Toxicities:<br>• Folate antagonists<br>• Bone marrow suppressant drugs | Monitor for toxicities of these drugs. |
| **Valacyclovir** | Potential For Increased Concentrations (of Both Drugs) and Overlapping Toxicity:<br>• Antivirals: acyclovir, valganciclovir, ganciclovir, cidofovir<br>• ARVs: tenofovir | Monitor for toxicities of these drugs. |
| **Valganciclovir** | Potential for Increased Concentrations (of Both Drugs) and Overlapping Toxicity:<br>• Antivirals: valacyclovir, acyclovir, ganciclovir, cidofovir<br>• ARVs: tenofovir | Monitor for toxicities of these drugs. |
| **Voriconazole** | Decreases Voriconazole Concentrations:<br>• Anticonvulsant drugs: carbamazepine, long-acting barbiturates | Caution advised. |
| | • Antimycobacterial drugs: rifabutin, rifampin | Rifabutin and Rifampin co-administration should be avoided. |
| | • ARV drugs: efavirenz, nevirapine, PIs boosted with ritonavir | Standard doses of efavirenz and voriconazole should not be used; voriconazole dose may need to be increased and efavirenz dose decreased, or use alternative antifungal agent.<br>Potential for increased PI concentrations and decreased voriconazole concentrations; consider monitoring voriconazole concentrations and adjust dose accordingly; monitor for PI-associated toxicities or consider using an alternative antifungal agent. |
| | Increases Voriconazole Concentrations:<br>• ARV drugs: etravirine | Monitor voriconazole concentrations to reduce toxicity. |
| | Increases Concomitant Drug Concentrations:<br>• Antimycobacterial drugs: rifabutin | Caution advised. |
| | • ARV drugs: protease inhibitors boosted with ritonavir, efavirenz, etravirine | Caution advised. |
| | • Statins: simvastatin, lovastatin, atorvastatin | Statins: Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy. |
| | • Sedatives/hypnotics: midazolam, alprazolam, triazolam | Co-administration should be avoided if possible. Monitor for toxicities. |

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; EKG = electrocardiogram; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; OI = opportunistic infection; PI = protease inhibitors; PK = pharmacokinetic; TDM = therapeutic drug monitoring

# Figure 1. Recommended Immunization Schedule for Children with HIV Infection Aged 0 through 18 Years; United States, 2019 (Last updated October 25, 2019; last reviewed October 25, 2019)

<table>
<tr><th>Vaccine ▼ Age ▶</th><th>Birth</th><th>1 month</th><th>2 months</th><th>4 months</th><th>6 months</th><th>9 months</th><th>12 months</th><th>13 months</th><th>15 months</th><th>18 months</th><th>19-23 months</th><th>2-3 yrs</th><th>4-6 yrs</th><th>7-10 yrs</th><th>11-12 yrs</th><th>13-14 yrs</th><th>15 yrs</th><th>16-18 yrs</th></tr>
<tr><td>Hepatitis B[1] (Hep B)</td><td>Hep B</td><td colspan="2">Hep B</td><td>See footnote 1</td><td colspan="6">Hep B</td><td colspan="8">Hep B Series</td></tr>
<tr><td>Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3 dose-series)</td><td></td><td></td><td>RV</td><td>RV</td><td>RV</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Diphtheria, tetanus & acellular pertussis[3] (DTaP: <7 yrs)</td><td></td><td></td><td>DTaP</td><td>DTaP</td><td>DTaP</td><td colspan="3">DTaP</td><td colspan="2">DTaP</td><td colspan="2">DTaP</td><td>DTaP</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Haemophilus influenzae type b[4] (Hib)</td><td></td><td></td><td>Hib</td><td>Hib</td><td>Hib</td><td>Hib</td><td colspan="6">Hib</td><td colspan="6">Hib</td></tr>
<tr><td>Pneumococcal conjugate[5] (PCV13)</td><td></td><td></td><td>PCV13</td><td>PCV13</td><td>PCV13</td><td>PCV13</td><td colspan="6">PCV13</td><td colspan="6">PCV13</td></tr>
<tr><td>Inactivated poliovirus[6] (IPV:<18 yrs)</td><td></td><td></td><td>IPV</td><td>IPV</td><td colspan="6">IPV</td><td colspan="2">IPV</td><td>IPV</td><td colspan="5">IPV</td></tr>
<tr><td>Influenza[7] (IIV)</td><td></td><td></td><td></td><td></td><td colspan="14">IIV (Yearly)</td></tr>
<tr><td rowspan="2">Measles, mumps, rubella[8] (MMR)</td><td></td><td></td><td></td><td></td><td></td><td></td><td>MMR</td><td colspan="5">MMR</td><td>MMR</td><td colspan="5">MMR</td></tr>
<tr><td colspan="18">Do not administer to severely immunocompromised children</td></tr>
<tr><td rowspan="2">Varicella[9] (Var)</td><td></td><td></td><td></td><td></td><td></td><td></td><td>Var</td><td>Var</td><td>Var</td><td colspan="9">Varicella</td></tr>
<tr><td colspan="18">Do not administer to severely immunocompromised children</td></tr>
<tr><td>Hepatitis A[10] (HepA)</td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">Hep A (2 doses)</td><td colspan="7">Hep A Series</td></tr>
<tr><td>Meningococcal[11] (MenACWY-D ≥9 mos; MedACWY-CRM ≥2 mos)</td><td></td><td></td><td colspan="16">MenACWY-CRM (through 23 months), MenACWY-D (9 months through 23 months)</td></tr>
<tr><td>Tetanus, diphtheria, & acellular pertussis[12] (Tdap: ≥7 years)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Tdap</td><td>Tdap</td><td colspan="3">Tdap</td></tr>
<tr><td>Human Papillomavirus[13] (9vHPV: males and females)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>HPV (3 doses)</td><td>HPV (3 doses)</td><td colspan="3">HPV (3 doses)</td></tr>
<tr><td>Meningococcal B[11]</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="5">MenB</td></tr>
<tr><td>Pneumococcal polysaccharide (PPSV23)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="7">PPSV23</td></tr>
</table>

Range of recommended ages for vaccination (yellow)

Catch-up immunization (green)

Certain high-risk groups (purple)

## Figure 1. Recommended Immunization Schedule for Children with HIV Infection Aged 0 through 18 Years; United States, 2019 (Last updated October 25, 2019; last reviewed October 25, 2019) (page 2 of 2)

This schedule summarizes recommendations for routine administration of vaccines for children with HIV aged 0 through 18 years and indicates the recommended ages for vaccine administration in this population for childhood vaccines licensed in the United States. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated, when other components of the vaccine are not contraindicated, and if approved by the Food and Drug Administration for that dose of the series. The combination measles, mumps, rubella, and varicella vaccine (MMRV) is an exception; in many circumstances measles, mumps, and rubella vaccine (MMR) and varicella vaccine (Var) should be administered to persons with immunocompetent HIV infection. MMRV is **contraindicated** in immunocompetent HIV infection. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at the VAERS website or telephone 1-800-822-7967.

These recommendations should also be used for children perinatally exposed to HIV who are awaiting laboratory confirmation that they have not contracted HIV; in the United States, HIV can be reasonably excluded in most HIV-exposed infants by 4 weeks of age (see the Department of Health and Human Services [HHS] Pediatric Antiretroviral Guidelines).

### 1. Hepatitis B Vaccine (HepB)

*Minimum Age: Birth*

At Birth:

- Administer monovalent HepB to newborns before hospital discharge. Normal-weight infants of mothers who are hepatitis B surface antigen (HBsAg)-negative should receive HepB within 24 hours of birth or at discharge, whichever comes first.
- If mother is HBsAg-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours after birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours after birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG **as soon as possible**. If the infant weighs <2,000 grams at birth, do not wait more than 12 hours after birth to administer HBIG. If the infant weighs ≥2,000 grams at birth, do not wait more than 7 days to administer HBIG.

After the Birth Dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 through 2 months.
- Monovalent HepB should be used for doses administered before age 6 weeks. The final dose should be administered no earlier than age 24 weeks. Infants who did not receive a HepB birth dose should receive three doses of a HepB- containing vaccine on an age-appropriate schedule.

Four-Month Dose:

- It is permissible to administer four doses of HepB when combination vaccines are administered after the birth dose. If monovalent HepB is used for doses after the birth dose, a dose at age 4 months is not needed.

Adolescents:

- Administer the series to those who were not previously vaccinated.

Post-Vaccination:

- Infants born to HBsAg-positive mothers should be tested for HBsAg and the antibody to HBsAg (anti-HBs) after completing at least three doses of a licensed HepB series, at ages 9 months through 12 months (generally at the next well-child visit).
- Testing for anti-HBs is also recommended for children and adolescents with HIV and should be performed 1 to 2 months after administration of the last dose of the vaccine series using a method that allows determination of a protective level of anti-HBs (≥10 mIU/mL).
- Children and adolescents with anti-HBs <10 mIU/mL after the primary schedule should receive a second series, followed by anti-HBs testing 1 to 2 months after the third dose.

Booster Dose:

- In children and adolescents with HIV, the need for booster doses has not been determined. Annual anti-HBs testing and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in individuals with ongoing risk for exposure (see https://www.cdc.gov/mmwr/pdf/rr/rr5416.pdf).

**2. Rotavirus Vaccine (RV)**

*Minimum Age: 6 Weeks*

- Practitioners should consider the potential risks and benefits of administering RV to infants with known or suspected altered immunocompetence. Consultation with an immunologist or infectious disease specialist is advised, particularly for infants with HIV infection who have a low CD4 T lymphocyte (CD4) cell percentage or count. Limited safety and efficacy data are available for the administration of RVs to infants who are potentially immunocompromised, including those with HIV infection. However, the following considerations support vaccination of infants who are HIV exposed or HIV infected:
    - In infants born to mothers with HIV, an HIV diagnosis may not be established before the age of the first RV dose (≤2% of infants with perinatal HIV exposure in the United States will eventually be determined to have HIV infection), *and*
    - Vaccine strains of rotavirus are considerably attenuated.
- RV can be administered to infants with HIV irrespective of CD4 count and percentage.
- The maximum age for the first dose in the RV series is 14 weeks and 6 days; for the final dose in the series, it is 8 months and 0 days. Vaccination **should not be initiated** for infants aged ≥15 weeks and 0 days.
- If Rotarix® is administered at ages 2 months and 4 months, a dose at age 6 months is not indicated.

**3. Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (DTaP)**

*Minimum Age: 6 Weeks*

- DTaP is recommended at ages 2, 4, 6, and 15 months through 18 months, and ages 4 through 6 years.
- The fourth dose may be administered as early as age 12 months, provided that at least 6 months have elapsed since the third dose.

**4. Haemophilus Influenzae Type B (Hib) Conjugate Vaccine**

*Minimum Age: 6 Weeks*

- If PRP-OMP (PedvaxHIB®) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- Children aged 12 months through 59 months who have received either no doses or only one dose of Hib vaccine before 12 months of age, should receive two additional doses of Hib vaccine 8 weeks apart;

children who received two or more doses of Hib vaccine before 12 months of age should receive one additional dose.

- One dose of Hib vaccine should be administered to persons aged 5 years through 18 years if they have not received a primary series and booster dose or at least one dose of Hib vaccine after 14 months of age.

5. **Pneumococcal Conjugate Vaccine (13-valent) (PCV13) and Pneumococcal Polysaccharide Vaccine (23-valent) (PPSV23)**

*Minimum Age: 6 Weeks for PCV13; 2 Years for PPSV23*

- A PCV series begun with 7-valent PCV (PCV7) should be completed with PCV13. For incompletely vaccinated children aged 24 months through 71 months, administer two doses of PCV13 ≥8 weeks apart. Children who have previously received three PCV13 doses need only one dose.
- A single dose of PCV13 should be routinely administered to children with HIV infection aged 6 years through 18 years who did not previously receive a dose of PCV13 before age 6 years. The dose should be administered ≥8 weeks after the previous dose of PCV.
- Children aged ≥2 years also should receive PPSV23 8 weeks after their last PCV dose. A second dose of PPSV23 should be administered 5 years after the first dose of PPSV23.

6. **Inactivated Polio Vaccine (IPV)**

*Minimum Age: 6 Weeks*

- If four or more doses are administered prior to age 4 years, an additional dose should be administered at age 4 years through 6 years.
- The final dose in the series should be administered on or after the child's fourth birthday and at least 6 months after the previous dose.

7. **Inactivated Influenza Vaccine (IIV)**

- Administer annually to children with HIV aged 6 months through 18 years and to all their eligible close contacts (including household members). IIV is recommended for children with HIV.
- Administer two doses (separated by at least 4 weeks) to children aged <9 years per current influenza vaccine recommendations.

8. **Measles, Mumps, and Rubella Vaccine (MMR)**

*Minimum Age: 12 Months*

- Two doses of MMR vaccine for all individuals with HIV infection aged ≥12 months who do not have evidence of current severe immunosuppression as defined by the Advisory Committee on Immunization Practices (see ACIP Recommendations for the Prevention of Measles Rubella Congenital Rubella Syndrome and Mumps).
- The first dose should be administered at age 12 months through 15 months and the second dose at age 4 years through 6 years (or as early as 28 days after the first dose).
- Individuals with perinatal HIV infection who were vaccinated prior to establishment of effective antiretroviral therapy (ART) should receive two appropriately spaced doses of MMR vaccine once effective ART has been established and there is no evidence of current severe immunosuppression as defined by ACIP (see https://www.cdc.gov/mmwr/pdf/rr/rr6204.pdf).

9. **Varicella Vaccine**

*Minimum Age: 12 Months*

- Limited data are available on safety and immunogenicity of varicella vaccine in children with HIV infection aged 1 year through 8 years in Centers for Disease and Control Prevention immunologic categories 1 and 2 (CD4 percentages ≥15%) and clinical categories N, A, and B.
- Single-antigen varicella vaccine should be considered for children and adolescents with HIV infection with CD4 percentages ≥15%.
- Eligible children should receive two doses 3 months apart.
- MMRV vaccine has not been studied in children or adolescents with HIV infection and should not be substituted for single-antigen varicella vaccine.

**10. Hepatitis A Vaccine (HepA)**

*Minimum Age: 12 Months*

- Administer to all children aged 12 months through 23 months. The two doses in the series should be administered ≥6 months apart.
- Children who are not fully vaccinated by age 2 years can be vaccinated at subsequent well-child visits.
- HepA is also recommended for persons aged ≥24 months who live in areas where vaccination programs target older children, who are at increased risk of infection, or for whom immunity against hepatitis A is desired—see Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the ACIP.

**11. Meningococcal Vaccine**

*Minimum Ages: 2 months for meningococcal conjugate vaccine (Menveo) (MenACWY-CRM); 9 months for meningococcal conjugate vaccine (Menactra) (MenACWY-D); 16 years for serogroup B meningococcal (Men B) vaccines, including (Bexsero) (MenB-4C) and (Trumenba) (MenB-FHbp); 10 years for HIV infection plus another high-risk condition for serogroup B meningococcal (MenB) vaccines, including (Bexsero) (MenB-4C) and (Trumenba) (MenB-FHbp)*

Meningococcal ACWY Conjugate Vaccines:

- Menveo
  - Children who initiate vaccination at 8 weeks: administer doses at 2, 4, 6 and 12 months of age.
  - Unvaccinated children who initiate vaccination at 7 through 23 months: administer two doses, with the second dose ≥12 weeks after the first dose AND after the first birthday.
  - Children aged ≥24 months who have not received a complete series: administer two primary doses ≥8 weeks apart.
- Menactra
  - Children aged ≥24 months who have not received a complete series: administer two primary doses ≥8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until age 2 years and at least 4 weeks after the completion of all PCV13 doses.

Meningococcal B Vaccines

*Clinical Discretion:*

- Young adults aged 16 years through 23 years (preferred age range is 16 years through 18 years) may be vaccinated with either a two-dose series of Bexsero or a three-dose series of Trumenba vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.
- For booster doses among persons with high-risk conditions, refer to Prevention and Control of

Meningococcal Disease.

**12. Tetanus and Diphtheria Toxoids and Acellular Pertussis Vaccine (Tdap)**

*Minimum Age: 7 Years*

- Children aged 7 years through 10 years who are not fully immunized against pertussis (i.e., have not received four or five doses of pertussis vaccine with the last dose administered on or after their fourth birthday) should receive a dose of Tdap after their seventh birthday. If Tdap is administered at age 7 years through 10 years, another dose of Tdap should be administered at 11 through 12 years of age.
- Individuals aged 11 through 18 years who have not received Tdap should receive a dose of the vaccine followed by tetanus and diphtheria vaccine (Td) booster doses every 10 years thereafter.
- Administer one dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred early during 27 through 36 weeks gestation) regardless of the time since prior Td or Tdap vaccination.

**13. 9-Valent Human Papillomavirus Vaccine (9vHPV)**

*Minimum Age: 9 years*

**Note:** Because 9vHPV is not a live virus vaccine, it can be administered to individuals who are immunosuppressed because of disease or medication, including those with HIV infection. However, the immune response and vaccine efficacy in immunosuppressed individuals may be less than in immunocompetent individuals.

- HPV vaccines are most effective for both males and females when given before exposure to HPV through sexual contact.
- Administer the first dose at age 11 or 12 years.
- Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (≥24 weeks after the first dose).
- Administer the series at ages 13 through 26 years if not previously vaccinated.
- HPV can be administered in a 3-dose series to individuals beginning at age 9 years.