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

Developed by 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) and in collaboration with the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics

How to Cite the Pediatric Opportunistic Infection Guidelines:

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

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

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What's New in the Guidelines

Updated: April 23, 2026
Reviewed: April 23, 2026

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 relevant outside reviewers before the document is altered. Major revisions within the last 6 months are as follows:

April 23, 2026

Mycobacterium avium *Complex Disease*

- Added linezolid, moxifloxacin, and bedaquiline as options for alternative therapy in children with severe symptoms or disseminated disease who need an alternative to rifabutin or a fourth drug as part of their treatment regimen.

Varicella-Zoster Virus Disease

- Added valacyclovir as preferred therapy in children aged ≥3 months with no or moderate immunosuppression diagnosed with uncomplicated herpes zoster or mild varicella.

- Clarified indications for passive immunization with varicella-zoster immune globulin (available as VariZIG) or intravenous immunoglobulin (or IVIG) after exposure to herpes zoster or varicella.

January 28, 2026

Hepatitis C Virus Infection

- Updated recommendations regarding breastfeeding in the setting of maternal HIV/hepatitis C virus coinfection to endorse shared clinical decision-making.

December 22, 2025

Candida *Infections*

- Updated information on the epidemiology of antifungal-resistant *Candida*, including *Candida auris*.

- Recommended posaconazole as an alternative therapy for fluconazole-refractory oropharyngeal candidiasis in children.
- Added isavuconazole as an alternative therapy for fluconazole-refractory esophageal candidiasis.
- Added information on the recommended management of *Candida* infections of the central nervous system.
- Emphasized the importance of antiretroviral therapy for all infants and children with HIV and candidiasis.

Human Papillomavirus Disease

- Updated the vaccine section to include information and recommendations on the nonavalent human papillomavirus (HPV) vaccine.
- Added a section on HPV vaccine efficacy.
- Expanded the section on treating HPV-associated warts, providing more detail on treatment considerations for children compared with considerations for older patients.

Pneumocystis *Pneumonia*

- Updated the age-specific criteria for discontinuing primary prophylaxis.
- Added guidance on *Pneumocystis jirovecii* pneumonia prophylaxis in breastfed infants with perinatal HIV exposure.
- Added intravenous pentamidine as an alternative regimen for primary prophylaxis.
- Added twice-daily dosing of atovaquone as an option for children aged 1 month to 12 years.

Toxoplasmosis

- Added information on the clinical manifestations of ocular toxoplasmosis.
- Updated the age-specific criteria for discontinuing and restarting primary and secondary prophylaxis.
- Updated the dosing recommendation for sulfadiazine secondary prophylaxis.
- Updated information on the preferred acute induction therapy regimen for treating acquired toxoplasmosis.

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 women 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 B: Moderate recommendation for the statement C: Optional recommendation for the statement	I: One or more randomized trials **in children**† with clinical outcomes and/or validated laboratory 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 clinical outcomes 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 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: 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). 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

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Immunizations for Preventable Diseases in Children and Adolescents With HIV

Updated: June 05, 2025
Reviewed: June 05, 2025

Immunizations are an extremely effective primary prevention tool, and vaccines that help protect against 19 diseases are recommended for routine use in children and adolescents in the United States. In addition, select immunizations may be recommended for children and adolescents with HIV in special circumstances (e.g., yellow fever vaccine [YFV] and cholera vaccine for international travelers). Immunization schedules for children from birth through 18 years of age are published annually by the Centers for Disease Control and Prevention (CDC). For more information see the following:

- Child and Adolescent Immunization Schedule by Age
- Child and Adolescent Immunization Schedule by Medical Indication
- ACIP Altered Immunocompetence Guidelines for Immunizations
- ACIP Vaccine Recommendations and Guidelines
- Interim Clinical Considerations for Use of COVID-19 Vaccines

These schedules are compiled from approved immunization-specific policy recommendations that are standardized in collaboration with the major immunization policy-setting and immunization-delivery organizations (i.e., the Advisory Committee on Immunization Practices [ACIP], American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Nurse Midwives, American College of Physicians, American Academy of Physician Associates, and National Association of Pediatric Nurse Practitioners). See the ACIP Recommendations webpage for recent updates.

It is critical that children and adolescents with HIV be vaccinated, as they are particularly vulnerable to severe complications from vaccine-preventable diseases. Most immunizations recommended for routine use can be administered safely to children with or exposed to HIV. The recommended immunization schedule for children aged 0 to 18 years with or exposed to HIV corresponds to the ACIP-approved schedule for all children and adolescents and includes ACIP-approved additions specific to children and adolescents with HIV that are summarized in Table 1 below. For more information, see Figure 1. Recommended Immunization Schedule for Children With HIV Infection Aged 0 Through 18 Years and CDC's Child and Adolescent Immunization Schedule by Medical Indication.

Table 1. Immunizations and Possible Variations for Children and Adolescents With HIV (Additional Vaccines Are Discussed in the Full Text)

Recommendation	Immunizing Agents
Immunization given according to routine schedule	Hepatitis B vaccine (HepB) Diphtheria, tetanus, acellular pertussis vaccine (DTaP) Tetanus, reduced diphtheria, reduced acellular pertussis vaccine (Tdap) Inactivated poliovaccine (IPV) Inactivated influenza vaccine (IIV) Hepatitis A vaccine (HepA) Nirsevimab
Precaution—immunization may be indicated when benefit of protection outweighs the risk	Rotavirus vaccine (RV) Dengue vaccine (DEN4CYD) *(only if CD4% ≥15% and total CD4 count of ≥200/mm^3)*
Immunization given according to routine schedule; additional doses may be needed	Haemophilus *influenzae* type b (Hib) Pneumococcal conjugate vaccine (PCV) Human papillomavirus vaccine (HPV) Meningococcal ACWY vaccine (MenACWY) Pneumococcal polysaccharide vaccine (PPSV) Monovalent COVID-19 vaccine (1vCOV-mRNA or 1vCOV-aPS)
Immunization given to individuals with an additional risk factor for which the vaccine would be indicated	Serogroup B meningococcal vaccine (MenB) Respiratory syncytial virus vaccine (RSVpreF) Mpox vaccine (Jynneos) Recombinant zoster vaccine (RZV)
Not recommended	Live attenuated influenza vaccine (LAIV) Oral typhoid vaccine (TY21A)
Not recommended if CD4% <15% and/or total CD4 count is <200 cells/mm^3	Measles-mumps-rubella vaccine (MMR) Varicella vaccine (VAR) Dengue vaccine (DEN4CYD)

Non-Live Vaccines

All non-live vaccines—whether killed, whole organism, or fractional vaccine—can be administered safely to individuals with altered immunocompetence. For children and adolescents without HIV, some non-live vaccines, such as pneumococcal conjugate vaccine (PCV) and *Haemophilus influenzae* type b conjugate vaccine (Hib), are not routinely recommended after certain ages, even if the recommended series was not completed. However, because children and adolescents with HIV have a risk of increased disease severity, these vaccines remain recommended beyond the routinely recommended ages for children and adolescents without HIV. For children and adolescents with HIV, some non-live vaccines are recommended as additional vaccine doses outside of the routine recommendation; for instance, an additional dose of mRNA COVID-19 vaccine can be administered to any person aged ≥6 months who has received a primary series and/or booster dose, as long as 2 months have elapsed since the most recent dose. Another example of additional vaccine doses is for children and adolescents with HIV who have received a complete primary series with PCV15 or PCV20 before 6 years of age. They can receive either one dose of PCV20 or one dose of pneumococcal polysaccharide vaccine (PPSV23), followed by either a second dose of PCV20 (after 8 weeks) or another dose of PPSV23 (after 5 years) if they are aged 2 years or older. Other non-live vaccines might be recommended outside the routine age window, such as quadrivalent meningococcal conjugate (MenACWY-CRM) vaccine beginning at age 2 months for children with HIV. Children with HIV aged 2 to 5 years who were partially vaccinated with a primary series of PCV13, 15, or 20 prior to their second birthday are recommended for catch-up doses of PCV15 or PCV20.

Live Vaccines

Certain live vaccines, such as live attenuated influenza vaccine (LAIV), are **contraindicated** for children and adolescents with HIV because of the potential risk of uninhibited vaccine microbe replication leading to adverse reactions. Annual age-appropriate influenza vaccination with non-live influenza vaccine is recommended for children and adolescents 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 with children and adolescents who are immunocompetent, children and adolescents with HIV are at higher risk for complications of some diseases for which only live vaccines are available. 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] Based on limited safety, immunogenicity, and efficacy data in children and adolescents with HIV, single-antigen varicella vaccine should be considered for children and adolescents with HIV and CD4 T lymphocyte (CD4) cell count percentages ≥15% of total lymphocytes (see Child and Adolescent Immunization Schedule by Medical Indication). Eligible children should receive two doses 3 months apart, with the first dose administered as soon as possible after the child's first birthday. In contrast, the measles, mumps, rubella, and varicella (MMRV) vaccine **should not be administered** to a child or adolescent with HIV, regardless of CD4 parameters.

Limited data are available from clinical trials on the safety of rotavirus vaccines in infants known to have HIV and 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 is different from that in infants who do not have HIV.[7,8] Two other considerations support rotavirus vaccination of infants with or exposed to HIV: first, the

diagnosis of perinatal HIV may not be established in infants born to mothers with HIV 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 milder than natural disease. Consultation with an immunologist or pediatric infectious disease specialist is advised before the rotavirus vaccine is administered to infants with known or suspected altered immunocompetence, such as infants with HIV with low CD4 counts (CD4 <200 cells/mm^3) or low CD4 percentages of total lymphocytes (CD4% <15%).

Oral typhoid vaccine **should not be administered** to children and adolescents with HIV. Intramuscular (IM) typhoid vaccine can be administered as an alternative. Ideally, travel vaccines should be administered 2 weeks prior to exposure or travel but should still be administered even if this window is shortened. Adequate prevention of typhoid disease requires, in addition to vaccination, education on food handling and other foodborne illness prevention.

The U.S. Food and Drug Administration has approved the cholera vaccine (Vaxchora–CVD 103-HgR) for children aged ≥2 years, adolescents, and adults. No safety or efficacy data exist regarding use of the current formulation of cholera vaccine in adults with HIV or people with severe immunosuppression. Limited data from an older formulation of the cholera vaccine suggest no association between the vaccine and serious or systemic adverse events, as well as slightly lower immunogenicity of the vaccine in adults with or without HIV. HIV infection is neither a contraindication nor a precaution to Vaxchora.[10]

If recommended, 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 cells/mm^3. Providers should ensure that patients do not have AIDS or other clinical manifestations of HIV, which are contraindications.

YFV is **contraindicated** for all children aged <6 months. YFV is also **contraindicated** for all children with symptomatic HIV or CD4 values <200 cells/mm^3 or <15% of total lymphocytes for children younger than 6 years. If a person with severe immunosuppression based on CD4 counts (<200 cells/mm^3 or <15% total), AIDS diagnosis, or symptomatic HIV cannot avoid traveling to an area in which yellow fever is endemic, a medical waiver for YFV should be provided, and counseling on protective measures against mosquito bites should be emphasized.

Precautions in administering YFV should be followed, and administering YFV may be considered for people with HIV who are aged ≥6 years with CD4 counts of 200 to 499 cells/mm^3 or children aged 6 months to 6 years with CD4 percentages of 15% to 24% of total lymphocytes. If international travel requirements, rather than an increased risk for acquiring yellow fever, are the only reason to vaccinate someone with a precaution, the person should be excused from vaccination and issued a medical waiver to fulfill health regulations. As with other travel vaccines, it is optimal to administer YFV 14 days before expected exposure.

At the time of the initial dose of YFV, people with HIV 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. (See the CDC Yellow Book and Yellow Fever ACIP Vaccination Recommendations for details on precautions and contraindications for YFV.) Of note, the YFV is only available at specialized centers, which can be found at CDC's Traveler's Health page.

Other Considerations

For certain vaccines (e.g., hepatitis A vaccine [HepA]), the response to vaccination may be greater with immune reconstitution following antiretroviral therapy (ART),[11] or immunogenicity may vary based on viral load (e.g., improved immune response with lower HIV viral load), such as with YFV.[12] Postvaccination serology is recommended for patients with HIV following HepA, and, if lower than 10 mIU/mL, revaccination with a series of HepA can be considered. After the second series, another serology can be performed, and if negative, no further doses are recommended, but counseling should be provided regarding the risks of hepatitis A and the need for immune globulin postexposure (see Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020.) For the hepatitis B vaccine, postvaccination serology is recommended for people with certain risk factors, including HIV, and revaccination is recommended if levels are lower than 10 mIU/mL.

For some additional vaccines, ACIP recommends performing postvaccination serology to ensure immune response. For most vaccines, people with higher CD4 counts have improved immune response, which also means that response (e.g., to vaccination for influenza, MMR, or yellow fever) likely would be improved after ART is initiated.[1,12-14] Concern about the lack of protection from vaccines administered before a child begins ART has prompted debate about the need for routine revaccination once a child is on effective ART.[12,15] Currently, the only vaccine for which there is a recommendation for revaccination is MMR, for which ACIP made specific recommendations for routine revaccination after initiation of ART.[5] This recommendation was based on the low rates of measles seroprotection in children with HIV who received the MMR vaccine before starting ART, as well as the safety and high rates of measles seroprotection associated with MMR revaccination after the children were receiving ART.[16] Individuals with perinatally acquired HIV who were vaccinated prior to establishment of effective ART should receive two appropriately spaced doses of MMR vaccine after effective ART has been established, unless they are severely immunosuppressed or have other acceptable current evidence of measles immunity.[5]

Household contacts of children and adolescents with HIV can be vaccinated with live vaccines because vaccination protects both the vaccine recipient and the child or adolescent by preventing transmission. Children and adolescents living in a household with an adult or child with HIV can receive the MMR vaccine because the viruses in this vaccine are not transmitted from person to person. All members of a household who are aged >6 months can receive yearly influenza vaccines. Likewise, household contacts of children and adolescents with HIV can receive the LAIV or the inactivated influenza vaccine (IIV); there is no preference between LAIV and IIV for household contacts of children and adolescents with HIV. Immunization against varicella is encouraged for all household contacts of children and adolescents with HIV without evidence of immunity to varicella.[16] Transmission of varicella vaccine virus from an immunized, immunocompetent individual to a household contact is rare. Household contacts of children and adolescents with HIV need special counseling if there is a need for live, replicating smallpox vaccine (ACAM2000), because contact between these children and adolescents should be avoided.

Although human papillomavirus (HPV) vaccines may be given on a two-dose schedule (0, >6 months) for immunocompetent individuals who initiate their HPV vaccinations between 9 and 14 years of age , a three-dose schedule (0, 1 to 2 months, >6 months) is recommended for all children and adolescents who are immunocompromised, including those with HIV.

Consult the specific ACIP statements (see ACIP Vaccine Recommendations and Guidelines) for more details regarding recommendations, precautions, and contraindications for use of specific vaccines (see CDC's MMWR, ACIP Updates: Recommendations for Use of 20-Valent Pneumococcal Conjugate Vaccine in Children — United States, 2023 **and** Use of 15-Valent Pneumococcal Conjugate Vaccine Among U.S. Children: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022 **and** Use of a 2-Dose Schedule for Human Papillomavirus Vaccination).[11,13,16-28]

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Bacterial Infections

Updated: November 21, 2024
Reviewed: November 21, 2024

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 children with HIV (AIII).
• Routine use of antibiotics solely for primary prevention of serious bacterial infections is not recommended (BIII). Discontinuation of antibiotic prophylaxis is recommended for children with HIV who are 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) (AII).
• Intravenous immune globulin is recommended to prevent serious bacterial infections in children with HIV who have hypogammaglobulinemia (IgG <400 mg/dL) (AI).
• Children with HIV whose immune systems are not seriously compromised (Stages 1 and 2) and who are not neutropenic can be expected to respond the same as children without HIV and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms (AIII).
• Severely immunocompromised children with HIV and invasive or recurrent bacterial infections require expanded empiric antimicrobial treatment covering a broad range of resistant organisms (AIII).
• Initial empiric therapy for children with HIV 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* or 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 postpubertal adolescents

Epidemiology

Before antiretroviral therapy (ART) was available, serious bacterial infections were the most commonly diagnosed opportunistic infections in children with HIV, with an event rate of 15 per 100 child-years.[1] Acute pneumonia, often presumptively diagnosed in children, was associated with increased risk of long-term mortality in children with HIV in one study from the pre-ART era.[2] Pneumonia was the most common serious bacterial infection (11 per 100 child-years), followed by bacteremia (3 per 100 child-years), and urinary tract infection (2 per 100 child-years).[1] Other serious bacterial infections—including osteomyelitis, meningitis, abscess, and septic arthritis—occurred at rates of <0.2 per 100 child-years.[1] Less serious bacterial infections, such as otitis media and sinusitis, were particularly common (17–85 per 100 child-years) in untreated children with HIV.[3]

Since the advent of combination ART in the late 1990s and universal guidelines recommending the rapid initiation of ART for all people with newly diagnosed HIV (including infants, children, and adolescents),[4,5] opportunistic infections among children with HIV in the United States have become exceedingly rare. Among children born during 1997 to 2016, the number of infants experiencing their first opportunistic infections decreased significantly from 432 during 1997 to 2001 to 24 during 2012 to 2016, with the biggest decrease in the number of diagnoses of *P. jirovecii* pneumonia (PCP).[6] Despite the overall decrease in the numbers of hospitalizations among children with HIV, the rates and adjusted odds of many bacterial outcomes (pneumonia, pneumococcal disease, bacterial infections/sepsis, methicillin-resistant *Staphylococcus aureus* [MRSA] infections) were still higher among hospitalized children with HIV compared with children without HIV from 2003 to 2012.[7] Additionally, children with HIV who are not receiving ART and present with pneumonia are more likely to be bacteremic and to die than children without HIV with pneumonia.[8,9] Children with chronic lung disease, including bronchiectasis and complicating repeated episodes of infectious pneumonia, also referred to as lymphocytic interstitial pneumonitis (LIP),[10,11] 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

Before the introduction of the first conjugate pneumococcal vaccine in the United States in 2000 and the use of ART in a substantial proportion of children with HIV in 1997, *S. pneumoniae* was the most prominent invasive bacterial pathogen in children with HIV, accounting for >50% of bacterial bloodstream infections in children with HIV.[1,12-14] Before the licensure of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000, the incidence of invasive pneumococcal disease (IPD) in children with HIV decreased by more than 80% from 1.9 per 100 person-years before ART to 0.3 per 100 in the ART era.[15] During the ART era, the rate of hospitalization for IPD in children and youth with HIV also declined by 62.5% since the introduction of PCV7.[16] Despite this significant decline in overall pneumococcal bacteremia, the odds of having pneumococcal disease as a discharge code was almost four times higher among children with HIV compared to children without HIV in 2012.[7] In children with IPD, study results vary on whether penicillin-resistant pneumococcal strains are more commonly isolated from people with HIV versus people without HIV, although these variabilities could reflect differences in the study setting.[17-20] 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 children without HIV[21]; however, most IPD in children with HIV is caused by susceptible pneumococci.[15] In 2010, PCV7 was replaced by a 13-valent pneumococcal conjugate vaccine (PCV13) for routine use in all children, including children with HIV.[22] Following the introduction of PCV13, the proportion of IPD caused by non-PCV13 serotypes increased.[23,24] The indications for 15-valent and 20-valent pneumococcal conjugate (PCV15 and PCV20) vaccines were recently expanded by the U.S. Food and Drug Administration in 2022 and 2023, respectively, for use in children aged 6 weeks and older,[25,26] thus providing an additional 10.6% to 38.2% coverage against IPD beyond serotypes contained in PCV13.[24] Among children with HIV, PCV15 elicited comparable levels of immunogenicity compared to PCV13 for the 13 shared serotypes[27] and was immunogenic for the two additional serotypes that are contained in PCV15. There has been reported variability in the efficacy of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in preventing IPD and pneumonia in adults with HIV.[28-30] The ultimate effectiveness of PCV15, PCV20, and PPSV23 in preventing IPD in children with HIV is not yet known. The current recommendation is for children to receive the four-dose series with PCV15 or PCV20; if PCV15 is used, a dose of PCV20 or PPSV23 should be given at least 8 weeks later.[31]

Haemophilus influenzae *Type b*

Children with HIV are at increased risk of invasive *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 had HIV than those who did not have HIV, and children with HIV were at greater risk for Hib bacteremic pneumonia.[32] Routine Hib immunizations in the United States and other countries has dramatically reduced invasive Hib infections in children.[33,34]

Neisseria meningitidis *(Meningococcus)*

HIV infection is associated with an increased risk of meningococcal disease.[35-39] In a population-based study of invasive meningococcal disease in New York City,[39] the average annual incidence rate of disease was high among people with HIV (15–64 years of age; 3.4 cases per 100,000 population) compared to people without HIV (0.34 cases per 100,000 population). As expected, the risk for invasive meningococcal diseases was 5.3 times higher among those with CD4 T lymphocyte (CD4) cell counts <200 cells/L compared with those with CD4 counts ≥200 cells/L. There are no studies of meningococcal disease risk in children with HIV 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 children with HIV were receiving ART at the time of this study.[35] A more recent population-based cohort study in the United Kingdom between 2011 and 2013 reported that children and adolescents with HIV had a higher risk of meningococcal group B disease, and adults were at increased risk of groups C, W, and Y disease.[37]

Methicillin-Resistant Staphylococcus aureus

HIV infection appears to be a risk factor for MRSA infections in children and adults, but findings are conflicting about the relative contribution of immunosuppression versus the impact of social determinants of health to this increased risk.[7,40-44] Limited data suggest that children with HIV, 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.[45] *S. aureus* (both methicillin-susceptible and MRSA) should be considered in people with a recent viral infection (especially influenza) or complicated pneumonia.

Other Pathogens

Other pathogens, including *Pseudomonas aeruginosa* and enteric organisms, cause infection in children with HIV, especially those who have indwelling vascular catheters or advanced immunosuppression or are not on ART.[13,46-49] The most commonly isolated pathogens in catheter-associated bacteremia in children with HIV are similar to those in children without HIV with indwelling catheters, including coagulase-negative staphylococci, *S. aureus*, enterococci, *P. aeruginosa*, gram-negative enteric bacilli, *Bacillus cereus*, and *Candida* spp.[12,48] In a cohort of 680 children with HIV in Miami, Florida, 10.6% had 95 episodes of gram-negative bacteremia between 1980 and 1997, of which 25% of children had two or three episodes of gram-negative bacteremia, and only six episodes were associated with an indwelling vascular catheter. The predominant organisms were *P. aeruginosa*, non-typhoidal *Salmonella*, and *E. coli* (15%).[46] 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.[47] Rates of bacterial enteric infections have declined substantially among people with HIV with the use of combination ART,[50] but should be considered in children with persistent diarrhea without an alternative etiology.[51] In most cases, the treatment of bacterial enteric infections in children with HIV does not differ from that of children without HIV. The optimal duration of treatment for *Salmonella* enteritis in children with advanced HIV has not been defined. Please refer to the American Academy of Pediatrics Red Book for more details on specific bacterial etiologies and their diagnosis and management.[52]

Please refer to the *Pneumocystis jirovecii* Pneumonia and *Mycobacterium avium* Complex Disease sections of the Pediatric Opportunistic Infections Guidelines for information on the prevention and treatment of these conditions.

Children Who Were Exposed to Maternal HIV (But Uninfected)

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, infants who were exposed to HIV but uninfected (HEU) had higher mortality (primarily because of bacterial pneumonia and sepsis) than did those born to uninfected mothers.[53-55] Observational studies from South Africa and Europe have also shown a higher risk of invasive Group B Streptococcus disease in children who were HEU compared to children without HIV exposure.[56-58] Advanced maternal HIV infection has been associated with infant mortality.[53,54] In a study in Latin America and the Caribbean, 61% of 462 infants who were HEU 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.[59] However, in a study from the United States, the rate of lower respiratory tract infections in children who were HEU was within the range reported for healthy children during the first year of life.[60] In a more recent study of children born during 2006 to 2017 in the United States, children who were HEU had approximately two times greater rates of infection-related hospitalization in the first 2 years of life compared to children who had not been exposed to HIV.[61] In addition to the potential of children who were HEU to experience increased severity in infections, data suggest that children who were HEU may be less likely to respond to treatment than children who have not been exposed to HIV, particularly in resource-limited settings.[62-64] There is increasing evidence for insufficient maternally derived antibody levels in infants who were HEU that put those infants at increased risk of pneumococcal and other vaccine-preventable infections.[65,66] However, at this time, there is no evidence to suggest that children who were HEU should receive vaccines on a different schedule from children without HIV exposure.

Clinical Manifestations

Clinical presentation depends on the particular type of bacterial infection (e.g., bacteremia/sepsis, osteomyelitis/septic arthritis, pneumonia, meningitis, sinusitis/otitis media)[67]; children with HIV who have an invasive bacterial infection typically have a clinical presentation similar to children without HIV.[68-70]

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 children with HIV who have reduced immune competence.[67,68] One-third of children with HIV not receiving ART who have acute pneumonia have recurrent episodes.[2] Bronchiectasis and other chronic lung damage that occurs before ART initiation can predispose an individual to recurrent pulmonary infections, even in the presence of combination ART.[10] Lower respiratory tract

bacterial infections in children with LIP most often are a result of the same bacterial pathogens that cause lower respiratory infection in children with HIV without LIP, manifesting as fever, increased sputum production, and respiratory difficulty superimposed on chronic pulmonary symptoms and radiologic abnormalities.[71]

In studies in Malawi and South Africa before the availability of ART, the clinical presentations of acute bacterial meningitis in children with and without HIV were similar.[72,73] However, in a study from Malawi, children with HIV were 6.4-fold more likely to have repeated episodes of meningitis than were children without HIV, although the study did not differentiate relapses from new infections.[72] In both studies, children with HIV were more likely to die from meningitis than were children without HIV.

Diagnosis

When evaluating children with HIV with a suspicion of a bacterial infection, pediatric infectious diseases should be consulted. Non-bacterial pathogens must also be considered as possible diagnoses in immunocompromised children with HIV.

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. Depending on its availability and pretest probability, molecular diagnostic testing of nasopharyngeal swabs, stool samples, or cerebrospinal fluid can be considered to aid in the diagnosis of children presenting with concerns for infection.[74-76] These molecular diagnostic testing panels also aid in the detection of antibiotic resistance markers, which can facilitate treatment management.[77]

In children presenting with respiratory symptoms, the diagnosis of pneumonia is often based on clinical symptoms and can be supported by an abnormal chest radiograph. The use of molecular diagnostic testing can aid in differentiating viral from bacterial pneumonia and has the potential to decrease hospitalizations and empiric antibiotic use.[78] Even after diagnosis with a viral infection, the clinician must consider that a secondary bacterial pneumonia can occur following the initial phase of a viral respiratory infection or during the recovery phase.[79] Blood and fluid from pleural effusion (if present) should be cultured. The differential for children with HIV and pneumonia must include *Mycobacterium tuberculosis* (TB) even if they are receiving ART, and must include PCP if they are not receiving combination ART. Presence of wheezing makes acute bacterial pneumonia less likely than other causes, such as viral infections, asthma exacerbation, atypical bacterial infections, or aspiration.[80] Children with LIP often have recurrent episodes of bacterial respiratory infection superimposed on chronic respiratory symptoms of cough and mild tachypnea.[81]

In children with bacteremia, a source should be sought. In addition to routine chest radiographs, other diagnostic imaging may be necessary in children with HIV with compromised immune systems to identify less apparent foci of infection (e.g., bronchiectasis, internal organ abscesses).[82-84] In children with suspected bacteremia and central venous catheters, blood culture should be obtained through the catheter and (if possible) peripherally.[85]

Prevention Recommendations

Children with HIV who are not receiving combination ART are at high risk for acquiring opportunistic infections. Regardless of their treatment status and CD4 count, children with well-

controlled HIV have a higher risk for certain infections, such as pneumococcal disease, compared to children without HIV.[86,87] The recommendations below are applicable to all children with or without HIV, but special considerations should be paid to children with HIV who are not receiving appropriate ART or are immunosuppressed.

Preventing Exposure

Because *S. pneumoniae* and *H. influenzae* (other than type b) commonly colonize the upper respiratory tract of children, no effective way exists to eliminate exposure to these bacteria. However, routine use of conjugated pneumococcal and Hib vaccines in the United States has dramatically reduced vaccine-type nasopharyngeal colonization in children, thus decreasing the risk of exposure to vaccine-type pathogens.[88-92]

Food

To reduce the risk of exposure to potential gastrointestinal bacterial pathogens, health care providers should advise that children with HIV 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).** Hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods to avoid unknowingly transferring bacteria from hands to chidren's food, milk, or formula or directly to children **(BIII).** Produce should be washed thoroughly before being eaten **(BIII).** These precautions are especially important for children who are not receiving combination ART.

Pets

When obtaining a new pet, caregivers should be aware that pets, especially puppies and kittens, can sometimes carry germs that can make people sick, even if the pet appears healthy. Proper veterinary care should be recommended for all pets to help ensure the risk of zoonotic disease transmission is minimized **(BIII).**[93] Children and adults with HIV should always wash their hands with soap and water after handling pets, especially before eating, and avoid contact with pets' feces **(BIII).**[94] Additionally, people with HIV should avoid contact with animals with diarrhea when possible; when not possible, they should use personal protective equipment like gloves. Due to the risk of infections such as salmonellosis, children younger than 5 years and immunosuppressed children should have limited exposure to reptiles (e.g., snakes, lizards, bearded dragons, turtles), live poultry (e.g., chicks, duckings), and rodents **(BIII).**[95,96] Reptiles and pet food should be kept out of the kitchen and anywhere that food is prepared, stored, served, or eaten to avoid cross-contamination of infectious pathogens. Any wounds sustained from pets, including bites or scratches that may seem minor, should be washed with warm soapy water immediately, and health care providers should be contacted.[97]

Travel

The risk of foodborne and waterborne infections in immunosuppressed people with HIV 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, cooked foods that have been allowed to cool without refrigeration, 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 safer include steaming hot foods, fruits that are peeled by the traveler, untampered 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.* However, iodine or chlorine treatment can be used when boiling is not practical.[98] These precautions are especially important for children who are not receiving combination ART.

Preventing Disease

Immunization

In addition to ART, one of the most important interventions to prevent bacterial infections in children with HIV is to ensure that they are immunized according to the HIV-specific recommended schedule (see the Center for Disease Control and Prevention's [CDC's] Child and Adolescent Immunization Schedule by Medical Indication) **(AII).**[99] Vaccines that protect against bacterial pathogens directly (e.g., pneumococcal, Hib, meningococcal, pertussis) and indirectly (e.g., influenza, COVID-19) have been demonstrated to be safe and immunogenic in children with HIV.[100-107] Children with HIV are at increased risk of under-immunization,[108] likely due to multiple factors, including those related to social determinants of health.[109] Therefore, vaccination status should be reviewed at every clinical encounter and indicated vaccinations provided, according to the established recommendations for immunization of children with HIV **(AIII).** Combination ART instituted before immunization offers the best means to optimize response to immunization.[110] Lack of combination ART and low CD4 counts may reduce the magnitude, quality, or duration of immunologic response and likely impair memory response. Greater number or strength of vaccine doses are recommended in some circumstances to overcome suboptimal response.

For the most up-to-date information on immunization, please refer to CDC's Child and Adolescent Immunization Schedule by Medical Indication.

Hib Vaccine

Children with HIV aged ≤5 years should receive Hib vaccine on the same schedule as that recommended for children without HIV, including for catch-up immunization **(AII).** See CDC's Child and Adolescent Immunization Schedule by Age for more information. Depending on the vaccine product, children should receive either a three-dose series with PedvaxHIB at ages 2 months, 4 months, and 12 to 15 months, or a four-dose series with ActHIB, Hiberix, Pentacel, or Vaxelis at ages 2 months, 4 months, 6 months, and 12 to 15 months. Vaxelis is not recommended for the fourth (booster) dose given at age 12 to 15 months; a different Hib-containing vaccine should be used.[111] Children with HIV between 1 and 5 years of age who have not received any Hib vaccine doses or who have only received one dose before the age of 12 months should receive two Hib vaccine doses 8 weeks apart. If they have received two or more doses before the age of 12 months, they should receive one additional dose at least 8 weeks after the previous dose. Children with HIV aged ≥5 years who have received less than the routine Hib series before age 14 months or have not previously received the Hib vaccine after age 14 months should receive one dose of any Hib conjugate vaccine **(AIII).**[112]

Pneumococcal Vaccines

Despite strong evidence on the efficacy of pneumococcal conjugate vaccine (PCV) among children (<7 years old) with and without HIV, its effectiveness against IPD among children with HIV was

notably limited in a meta-analysis of 10 studies that were mainly from South Africa.[113] As of June 2023, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended the use of PCV15 or PCV20 for routine vaccination in children <2 years.[114] Children with HIV aged <2 years should receive routine pneumococcal conjugate vaccines (either PCV15 or PCV20) on the same schedule as that recommended for children without HIV **(AII).**[31] A four-dose series of either PCV15 or PCV20 is recommended for routine administration to children aged 2 months, 4 months, 6 months, and 12 to 15 months.

Children aged 2 to 6 years with HIV who have incomplete PCV vaccination status should receive either PCV15 or PCV20 according to currently recommended dosing and schedules. If they have received three conjugate vaccine doses before age 12 months but have not received their fourth booster dose, they should receive an additional dose at least 8 weeks after any prior PCV15 or PCV20 dose. If they have received any incomplete schedule of fewer than three conjugate vaccine doses before age 2 years, they should receive two doses of PCV15 or PCV20 (8 weeks after the most recent dose and administered 8 weeks apart).[20]

In addition, children with HIV aged ≥2 years who have received all recommended PCV doses using PCV13 or PCV15 should receive either a dose of PCV20 or PPSV23 (≥8 weeks after their last PCV dose). If PPSV23 is administered, either a dose of PCV20 or a second dose of PPSV23 is recommended 5 years after the first PPSV23 **(AII).**[31] Children with HIV aged ≥2 years who have received at least one dose of PCV20 do not need additional pneumococcal vaccine doses. Children with HIV aged 6 to 18 years with no prior history of PCV13, PCV15, or PCV20 should receive one pneumococcal conjugate vaccine dose (PCV15 or PCV20). If PCV15 is used, it should be followed by a dose of PPSV23 at least 8 weeks later if not previously given.[114]

Meningococcal Vaccine

All children with HIV age ≥2 months should routinely receive the age-appropriate series of the meningococcal ACWY (MenACWY) conjugate vaccine **(AIII).**[115] In contrast to the two-dose primary series for adolescents without HIV, children with HIV aged <2 years should be vaccinated according to the age-appropriate multidose schedule with MenACWY-CRM (Menveo) (see CDC's Child and Adolescent Immunization Schedule by Medical Indication). Children with HIV aged ≥2 years who have not received any meningococcal conjugate vaccines should receive a primary series of MenACWY conjugate vaccine of two doses given at least 8 weeks apart.[115] For booster doses, children aged <7 years should get a single dose at 3 years after the primary series and every 5 years thereafter. Children aged ≥7 years should receive a single dose at 5 years after primary vaccination and every 5 years thereafter.[115]

At this time, serogroup B meningococcal (MenB) vaccine is not routinely indicated for children with HIV, but may be administered to persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease (e.g., persons with complement deficiencies) and is recommended for adolescents ≥16 years on the basis of shared clinical decision-making.[116]

Influenza Vaccine

Because influenza increases the risk of secondary bacterial respiratory infections,[117,118] annual influenza vaccination for influenza prevention can be expected to reduce the risk of serious bacterial infections in children with HIV **(AIII).**[119] Children with HIV should receive annual influenza vaccination according to the HIV-specific recommended immunization schedule **(AII)** (see CDC's Child and Adolescent Immunization Schedule by Medical Indication).[120] Live attenuated influenza

vaccines are contraindicated in people with HIV; children with HIV should receive inactivated influenza vaccines.[121]

COVID-19 Vaccine

COVID-19 has been associated with bacterial coinfections, and a bacterial coinfection with COVID-19 is a major risk of mortality and morbidity.[122-124] All children with HIV should receive the COVID-19 vaccine regardless of their CD4 count or HIV viral load; for current COVID-19 vaccination recommendations, please visit the Interim Clinical Considerations for Use of COVID-19 Vaccines in the United States.

Chemoprophylaxis

Among children with HIV who have an indication for PCP prophylaxis, daily trimethoprim-sulfamethoxazole (TMP-SMX) may decrease the rate of serious bacterial infections (predominantly respiratory) **(BII).**[125,126] For people who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone **(BI*),** aerosolized pentamidine with a Respirgard II nebulizer **(BI*),** and atovaquone plus azithromycin **(AI).** Atovaquone combined with azithromycin, which provides prophylaxis for *Mycobacterium avium* complex (MAC) as well as PCP, is well tolerated, and is as effective as TMP-SMX in preventing serious bacterial infections in children with HIV.[127] For more detail on when to initiate primary prophylaxis, please refer to the *Pneumocystis jirovecii* Pneumonia and *Mycobacterium avium* Complex Disease sections of the Pediatric Opportunistic Infection Guidelines. 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 therefore not routinely recommended **(BIII).** Intravenous immune globulin (IVIG) is recommended to prevent serious bacterial infections in children with HIV who have hypogammaglobulinemia (immunoglobulin G <400 mg/dL) **(AI).**[128]

Discontinuation of Primary Prophylaxis

The Pediatric AIDS Clinical Trials Group (PACTG) Protocol 1008 demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in children with HIV who achieved sustained (≥16 weeks) immune reconstitution (CD4 cell percentage >20% to 25%) while receiving ART did not result in excessive rates of serious bacterial infections.[129] In support of discontinuing primary prophylaxis, multiple observational and randomized studies in adults have demonstrated a low incidence of PCP and MAC in adults who discontinued prophylaxis after receiving ART with sustained CD4 count recovery for >3 months.[130-133] Antibiotics for primary prophylaxis of serious bacterial infections should be discontinued in children with HIV once they have achieved sustained (i.e., ≥3 months) immune reconstitution (CD4 percentage ≥25% if aged <6 years; CD4 percentage ≥20% or CD4 count >350 cells/mm^3 if aged ≥6 years) **(AII).**

Treatment Recommendations

Treating Disease

The principles for treating serious bacterial infections are the same in children with and without HIV. Specimens for microbiologic studies should be collected before initiation of antibiotic treatment. However, in those with suspected serious bacterial infections, therapy should be administered empirically and promptly without waiting for the 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 should be based on the results of susceptibility testing **(AIII).** The involvement of antibiotic stewardship programs when managing people with bacterial infections is also essential in ensuring appropriate antibiotic use and making sure that the development of antibiotic resistance is minimized.[134,135]

Children with HIV whose immune systems are not seriously compromised (Stages 1 and 2; see HIV Infection Stage table in the Introduction) and who are not neutropenic can be expected to respond similarly to children without HIV, and they should be treated for the most likely bacterial organisms **(AIII).** Based only on expert opinion, mild-to-moderate community-acquired pneumonia in children with HIV on ART with only mild or no immunosuppression who are fully immunized (especially against *S. pneumoniae* and Hib) can be treated with oral antibiotics (usually oral amoxicillin) according to the same guidelines as for healthy children **(BIII).** 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 children with HIV.[15,17-19,136,137] Thus, options for empiric therapy for children with HIV outside of the neonatal period who are hospitalized for suspected community-acquired bacterial pneumonia or bacteremia include ampicillin or an extended-spectrum cephalosporin (e.g., ceftriaxone), respectively **(AIII).**[138-140] The addition of vancomycin or other antibiotic for suspected bacterial meningitis should follow the same guidelines as for children without HIV.[141] The addition of a macrolide or fluoroquinolone can be considered for hospitalized individuals 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, TMP-SMX, or vancomycin can be added (choice based on local susceptibility patterns and adjusted according to culture results).[142-146] Neutropenic children also should be treated with an appropriate antipseudomonal drug if infection with *Pseudomonas* spp. is likely. Severely immunocompromised children with HIV and 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 children with HIV with suspected intravascular catheter sepsis should target both gram-positive and enteric gram-negative organisms, with combinations that include agents with anti-*Pseudomonas* activity (e.g., ceftazidime, cefepime) and vancomycin **(AIII),** taking into consideration the person's history of drug-resistant infections or colonization. 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.[85]

Monitoring and Adverse Events (Including IRIS)

The response to appropriate antibiotic therapy should be similar in children with and without HIV. A clinical response is usually observed within 2 to 3 days after initiation, and radiologic improvement in individuals with pneumonia may lag behind clinical response.

Immune reconstitution inflammatory syndrome (IRIS) has not clearly been described in association with treatment of typical bacterial infections in children. Reports of bacterial infections in children during the first several weeks of combination ART have been associated with IRIS;[147,148] however, more recent data report mycobacterial (e.g., TB) and non-bacterial causes (e.g., cytomegalovirus,

cryptococcal meningitis) to be more commonly attributed to IRIS.[149] 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, influenza and COVID-19 should be reviewed and updated, according to the recommendations outlined above and in the HIV-specific recommended immunization schedule from the Panel and ACIP **(AIII).** Refer to CDC's Child and Adolescent Immunization Schedule by Medical Indication for more information.

Among children with HIV who have an indication for PCP or MAC secondary prophylaxis, TMP-SMX (administered daily or three times per week for PCP prophylaxis) with either azithromycin or clarithromycin (administered for MAC prophylaxis) may reduce the recurrence of serious bacterial infections. Administration of antibiotic chemoprophylaxis to children with HIV who have frequent recurrences of serious bacterial infections despite ART (e.g., more than two serious bacterial infections in a 1-year period despite ART) can be considered **(CIII);** however, caution is required when using antibiotics solely to prevent recurrence of serious bacterial infections because of the potential for developing drug-resistant microorganisms and drug toxicity. In rare situations in which ART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis **(CI).**[128]

Discontinuing Secondary Prophylaxis

PACTG 1008 demonstrated that discontinuing MAC and/or PCP antibiotic prophylaxis in children with HIV who achieved sustained (i.e., ≥16 weeks) immune reconstitution (CD4 percentage >20% to 25%) while receiving ART did not result in excessive rates of serious bacterial infections.[129] In support of discontinuing secondary prophylaxis, multiple observational and randomized studies in adults demonstrated a low incidence of PCP and MAC in individuals who discontinued prophylaxis after receiving ART with sustained CD4 cell count recovery for >3 months.[131,132,150,151] Antibiotics for secondary prophylaxis of serious bacterial infections should be discontinued in children with HIV who have achieved sustained (i.e., ≥3 to 6 months) immune reconstitution (CD4 percentage ≥25% if ≤6 years old; CD4 percentage ≥20% or >350 cells/mm^3 if >6 years old) **(AII).**

Dosing Recommendations for Prevention and Treatment of Invasive Bacterial Infections

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis *S. pneumoniae* and other invasive bacteria	• Pneumococcal, meningococcal, and Hib vaccines • IVIG 400 mg/kg body weight every 2–4 weeks (only in cases of hypogammaglobulinemia, IgG <400 mg/dL)	TMP-SMX 75/375 mg/m^2 body surface area per dose by mouth twice daily	See CDC website for detailed immunization schedule. Criteria for Discontinuing IVIG • Resolution of hypogammaglobulinemia Criteria for Restarting IVIG • Relapse of hypogammaglobulinemia
Secondary Prophylaxis *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 • More than two serious bacterial infections in a 1-year period in children who are unable to take ART Criteria for Discontinuing Secondary Prophylaxis • 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) Criteria for Restarting Secondary Prophylaxis • More than two serious bacterial infections in a 1-year period despite ART
Treatment Bacterial pneumonia; *S. pneumoniae*; occasionally *S. aureus*, *H. influenzae*, *P. aeruginosa*	• Amoxicillin 90 mg/kg/dose orally divided every 8 or 12 hours (max 1 g/dose) for outpatient management, *or* • Ampicillin 200–400 mg/kg/day divided every 6 hours (max 2 g/dose) (use higher dose if *S. pneumoniae* MIC ≥4 mcg/mL), *or* • 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)	• Ceftazidime 200–300 mg/kg/day divided every 8 hours IV or IM (max 12 g/day), *or* • Cefepime 50 mg/kg/dose every 8 hours IV or IM (max 2 g/dose)	Alternative treatment should be determined based on local antimicrobial susceptibility patterns or that of the bacterial isolate, if available. For children who are receiving combination ART, have mild or no immunosuppression, and have mild-to-moderate community-acquired pneumonia, oral therapy option would be amoxicillin 45 mg/kg/dose twice daily (maximum dose: 4 g per day). Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (*M. pneumoniae, C. pneumoniae*).

Indication	First Choice	Alternative	Comments/Special Issues
			Add clindamycin or vancomycin if methicillin-resistant *S. aureus* is suspected (base the choice on local susceptibility patterns). For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (such as ceftazidime or cefepime instead of ceftriaxone). Consider PCP in patients with severe pneumonia or more advanced HIV disease. Evaluate for tuberculosis, cryptococcosis, and endemic fungi as epidemiology suggests.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; Hib = *Haemophilus influenzae* type b; IgG = immunoglobulin G; IM = intramuscular; IV = intravenous; IVIG = intravenous immune globulin; LIP = lymphocytic interstitial pneumonia; MIC = minimum inhibitory concentration; PCP = *Pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole

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Candida Infections

Updated: December 22, 2025
Reviewed: December 22, 2025

Panel's Recommendations

Oropharyngeal Candidiasis

- Topical therapy using clotrimazole troches or nystatin suspension for 7–14 days is recommended to treat uncomplicated oropharyngeal candidiasis (OPC) (AI*).
- Oral fluconazole for 7–14 days is recommended for moderate to severe OPC disease (AI).
  - For fluconazole-refractory OPC, itraconazole oral solution is recommended, although itraconazole is less well tolerated than fluconazole (AI*). Posaconazole is an alternative, particularly for fluconazole- and itraconazole-refractory OPC (AI*).
- Chronic suppressive therapy for OPC is not routinely recommended (AII*), as treatment of recurrence is typically effective and potential risks include toxicities, resistance, drug–drug interactions, adherence challenges, and costs; the primary modality of preventing recurrences is immune reconstitution via antiretroviral therapy. If required on a case-by-case basis (e.g., due to frequent or severe recurrences despite antiretroviral therapy), fluconazole three times weekly is preferred (AI*).

Esophageal Candidiasis

- Systemic therapy is always required for esophageal disease (AI*).
- Oral fluconazole for 14–21 days is recommended as first-line therapy, but intravenous fluconazole, an echinocandin (caspofungin, micafungin, anidulafungin), or amphotericin B[a] can be used in those who cannot tolerate oral therapy (AI*).
- For refractory esophageal disease, oral therapy should include itraconazole solution or voriconazole for 14–21 days (AI*).
- If required, suppressive therapy with fluconazole three times weekly is recommended for recurrent infection, pending immune reconstitution on antiretroviral therapy (AII*).

Invasive Candidiasis

- 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 (AI*).
- Alternatively, an initial course of amphotericin B[a] therapy can be administered for invasive candidiasis (BI*) with careful transition to fluconazole therapy to complete the treatment course (BII*).
- For central nervous system (CNS) candidiasis, initial treatment should use amphotericin B[b] (AIII).
- Children with candidemia should be treated for ≥14 days after documented clearance of *Candida* from the last positive blood culture, resolution of neutropenia, and resolution of clinical signs and symptoms of candidemia (AIII).
- Central venous catheters should be removed when feasible in children with candidemia (AII*). For CNS candidiasis, infected CNS devices should be removed if possible (AIII).

Antiretroviral Therapy

- Antiretroviral therapy should be initiated in all infants and children with HIV, particularly those with candidiasis (AI for children aged <3 months, AI* for older children).

[a] Amphotericin B lipid formulations are generally preferred in children based on non-inferior efficacy and lower toxicity compared to conventional amphotericin B (deoxycholate), particularly in children who are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (AI). Amphotericin B deoxycholate is acceptable if a lipid formulation is unavailable or infeasible (BI*).

[b] For initial treatment in neonates, amphotericin B deoxycholate or liposomal amphotericin B (caution with suspected urinary tract involvement) is recommended (BIII). Beyond the neonatal/infant period, liposomal amphotericin B is recommended with or without flucytosine (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 postpubertal adolescents

Epidemiology

The most common fungal infections in children with HIV are caused by *Candida* spp. Antifungal-resistant *Candida* is a public health threat that was exacerbated by the COVID-19 pandemic. The Centers for Disease Control and Prevention (CDC)'s 2022 special report on COVID-19's U.S. impact on antimicrobial resistance identified that previously decreasing U.S. trends in cases of antifungal-resistant *Candida* had reversed, with a 1-year 26% increase in hospital-onset antifungal-resistant *Candida* in 2020 (28,100 drug-resistant cases total, 12,900 hospital-onset cases), while antifungal-resistant *C. auris* continued to increase in cases, with a 1-year 60% increase to 754 U.S. cases.[1] In 2022, the World Health Organization (WHO) released its first fungal priority pathogens list as the first global effort to systematically prioritize fungal pathogens concerning their unmet research and development needs and their perceived public health importance. *C. auris and C. albicans* were included in the critical priority group, and *C. glabrata (Nakaseomyces glabrata)*, *C. tropicalis*, and *C. parapsilosis* were included in the high priority group.[2] These developments have highlighted the importance of diagnosing, preventing, and treating pediatric candidiasis.

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. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent opportunistic infections in children with HIV in the United States during the antiretroviral therapy (ART) era (in the pre-ART era, 28% of children with HIV had a history of OPC), with an incidence rate of 0.93 per 100 child-years.[3] In high

HIV-burden regions from 2004 through 2016, OPC remained the most common incident non-tuberculous WHO stage 3 (WHO-3) event in children, constituting 46% of such events in the pre-ART era (7.0 WHO-3 events per 100 child-years) and 31% of such events in the ART era (2.1 WHO-3 events per 100 child-years).[4] In children with HIV in the United States, the incidence of esophageal or tracheobronchial candidiasis decreased from 1.2 per 100 child-years before the pre-ART era to 0.08 per 100 child-years during the ART era (2001–2004).[3] Based on data from the CDC's National HIV Surveillance System through 2018, among children with HIV and born between 1997 to 2016, the numbers and rates of all opportunistic infections (OIs) decreased over time, but pulmonary or esophageal candidiasis remained the second-most common OI among children (15.4% of OIs) in the more recent cohort (born 2007–2016).[5] *Candida* esophagitis continues to be seen in children who are not responding to ART.[6,7] Children who develop esophageal candidiasis despite ART may be less likely to have typical symptoms (e.g., odynophagia, retrosternal pain) or have concomitant OPC[8]; during the pre-ART era, concomitant OPC occurred in 94% of children with *Candida* esophagitis.[6] 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).[3,6,7,9]

Invasive Candidiasis

Invasive candidiasis is less frequent than localized disease in children with HIV. However, *Candida* can disseminate from the esophagus, particularly during coinfection with herpes simplex virus (HSV) or cytomegalovirus (CMV).[6,10] Candidemia occurs in up to 12% of children with HIV who have chronic indwelling central venous catheters placed for administration of total parenteral nutrition or intravenous (IV) antibiotics.[7,11] 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 most bloodstream infections.[12,13] 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 resistance to both fluconazole and voriconazole. An increasing number of *C. glabrata* isolates are also resistant to echinocandins. *C. lusitaniae* frequently have or acquire resistance to amphotericin B.[14-16] 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.[7] In one study of Cambodian children with HIV 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.[17] However, clinicians should be aware of local resistance trends as the epidemiology of species-specific resistance may vary widely by geographic location and hospital.

Although uncommon in children in the United States, *C. auris* is an important emerging fungal pathogen because it is often multidrug resistant, spreads easily in health care facilities, and can cause severe, invasive infections with high mortality.[18-20] In cases reported to U.S. state and local health departments and the CDC from 2016 to 2021, *C. auris* clinical cases and screening cases have increased in frequency and geographical distribution.[21] In 2020, azole resistance was high (86% of isolates) and amphotericin B resistance was common (26% of isolates), although susceptibility patterns varied by U.S. geographical regional in association with local circulation of specific clades. Echinocandin resistance across all clades and geographical regions has been low (<5%), but echinocandin-resistant and pan-resistant isolates have been reported and increased in 2021.[21-23]

Almost all reported U.S. *C. auris* cases have been in adults, but a cluster of pediatric *C. auris* was identified in two health care facilities where procedural areas were shared between children and adults. Although no direct transmission link was identified, the cases highlight the potential for *C. auris* spread from adults to children.[24,25]

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 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.[7]

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[7] or automated broth-based systems.[26] When candidemia is present, particularly among immunocompromised children or those with persistent candidemia, further investigation for dissemination should strongly be considered **(AII).** Additional diagnostics that should be considered in this clinical scenario include, but are not limited to, fundoscopic exam for intraocular infection, a lumbar puncture for central nervous system (CNS) disease; an echocardiogram for endocarditis; an abdominal ultrasound or computed tomography to evaluate the kidney, liver and spleen; and magnetic resonance imaging for osteomyelitis (if suspected by symptoms) or bone scans (if suspecting multifocal disease). In a multicenter cohort study of 662 pediatric candidemia episodes, use of adjunctive diagnostic studies varied across sites.[27] Longer durations of candidemia, immunocompromised status (not specific to HIV), and intensive care at candidemia onset were associated with use of adjunctive diagnostic studies. Positive findings were reported in 3% of ophthalmic exams, 6% of abdominal imaging, 3% of echocardiograms, 6% of neuroimaging, and 4% of lumbar punctures. Pediatric participants with

immunocompromise or persistent or relapsed candidemia more commonly had positive findings. Notably, ophthalmic exams had positive findings in only 1% of non-immunocompromised participants,[27] which was consistent with a systemic review of adults and pediatric patients with candidemia.[28] Similar risk factors for dissemination, including prolonged candidemia (especially with a central venous catheter), prematurity, and immunocompromised status, were identified in single-center studies previously.[29-32] The utility of universal ophthalmic examinations in settings of candidemia has been subject to discrepant opinions by professional societies across disciplines.[28,33,34] Data are limited regarding the optimal indications and visual outcomes following ophthalmologic screening in children with candidemia. However, the available data suggest that ophthalmic screening may be most useful in children with prolonged candidemia, immunocompromised status (including prematurity), more severe illness or other evidence of dissemination, or those unable to verbalize symptoms or indicate signs of ocular disease. As most neonates, infants, and children fall into the last category, a universal ophthalmic screening approach remains a reasonable option. Management of these populations should involve collaboration among primary providers, infectious diseases physicians, and ophthalmologists.

Diagnostic techniques such as the *Candida* mannan antigen and anti-mannan antibody,[35,36] (1,3)-beta-D-glucan assay,[37,38] T2 biosystems for *Candida*,[39] real-time polymerase chain reaction,[40,41] and next-generation sequencing for microbial cell-free DNA[42-44] are diagnostic alternatives for invasive candidiasis. As newer diagnostic modalities become more accessible, a pediatric infectious diseases specialist should be involved in decisions about the use of certain novel diagnostics (e.g., microbial cell-free DNA), which may have high costs,[45] unclear roles in diagnostic algorithms, and undetermined applicability to specific pediatric populations with varying immunocompromising disease states. Although several of these assays are helpful in diagnosing invasive candidiasis in adults, only a few have been studied in children, and performance characteristics in adults have not necessarily translated into pediatric populations. A multicenter prospective observational cohort study of 500 children without HIV aged >120 days to <18 years at 22 centers in three countries evaluated the performance characteristics of the T2Candida, Fungitell (1→3)-β-D-glucan, Platelia *Candida* Antigen Plus, and Platelia *Candida* Antibody Plus assays for detection of candidemia. This study used a reference standard of proven or probable invasive candidiasis as defined by the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for invasive fungal disease made on or between Day 0 through Day 14 of study.[46] Of these biomarkers, T2Candida had the highest sensitivity (79.2%) and specificity (97.1%) and was the only biomarker with sufficient performance characteristics to be considered as an individual tool for diagnosis of candidemia in at-risk children and adolescents. However, combining T2Candida with the Platelia *Candida* Antigen assay could provide additional optimization according to the specific goals of the clinical situation.

Prevention Recommendations

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals; thus, complete prevention of exposure may not be feasible. However, some measures may decrease *Candida* colonization or overgrowth, such as avoiding unnecessary antibiotics (especially broad-spectrum antimicrobial agents) or minimizing use of systemic corticosteroids, if able. Maintaining good oral health, hygienic care for central venous or peritoneal dialysis catheters, and management of predisposing comorbid conditions, such as diabetes mellitus, should also be beneficial.[47]

Preventing First Episode of Disease

Routine primary prophylaxis of candidiasis in infants and children with HIV 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, concern for potentiating resistant *Candida* strains, and the potential for drug–drug interactions between antifungal and antiretroviral (ARV) agents.[48] If a child with HIV has a comorbid condition (e.g., prolonged, severe neutropenia), then primary prophylaxis should be guided by recommendations for management of children with the comorbid condition.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Oropharyngeal Candidiasis

For early, uncomplicated infection, topical therapy using clotrimazole troches or oral nystatin suspension for 7 to 14 days is recommended **(AI*).**[49-57] 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.[58]

Systemic therapy with one of the oral azoles (e.g., fluconazole, itraconazole, posaconazole) for 7 to 14 days is recommended for moderate to severe OPC.[34,49-51] 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 **(AI).**[50,53]

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 **(AI*).**[59,60] 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. Therefore, itraconazole capsules are **not recommended** for treating OPC if fluconazole or itraconazole solutions are available **(AII),** although itraconazole tablets may retain a role when administration of itraconazole solution is impractical (e.g., volume, intolerance considerations). Posaconazole is a second-generation orally bioavailable triazole. Randomized clinical trial data of adults with HIV allocated to either posaconazole or fluconazole for primary treatment of OPC demonstrated that posaconazole was as effective as fluconazole in producing a successful clinical outcome (91.7% vs. 92.5%, 95% confidence interval [CI], –6.6 to 5.0), but posaconazole was more effective in clinical success after treatment was stopped, with greater mycological success at Day 42 (40.6% vs. 26.4%) and fewer recipients with clinical relapse (31.5% vs. 38.2%).[61] Posaconazole has also been effective in adolescents and adults with HIV who have fluconazole- and itraconazole-refractory OPC or esophageal candidiasis.[62,63] Although experience in children is still limited, newer posaconazole formulations provide more consistent absorption and drug exposures or the option of IV therapy.[63,64] Thus,

posaconazole is recommended as an alternative for OPC in children, particularly for fluconazole- and itraconazole-refractory OPC **(AI*).** Additional choices for fluconazole-refractory OPC include voriconazole, an echinocandin (caspofungin, micafungin, anidulafungin), or amphotericin B, if required.

Esophageal Disease

Systemic therapy is essential for esophageal disease **(AI*)** and should be initiated empirically in children with HIV who have OPC and esophageal symptoms. In most children and adolescents, 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 **(AI*).**[34,65] For individuals who cannot tolerate oral therapy, IV fluconazole, an echinocandin, or amphotericin B should be used **(AI*).**

For fluconazole-refractory disease, oral therapy can include itraconazole solution or voriconazole for 14 to 21 days **(AI*).**[65,66] Approximately 50% to 60% of individuals with fluconazole-refractory OPC and 80% of individuals with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution.[67,68] Voriconazole has supporting randomized control trial data in immunocompromised adults (most with HIV) demonstrating that voriconazole is at least as effective as fluconazole in treatment of biopsy-proven esophageal candidiasis (98.3% vs. 95.1%; 95% CI, −1.0 to 7.5), but adverse events (AEs) associated with voriconazole were more frequent and interindividual variability in pharmacokinetics is high.[66] In a study of voriconazole in children aged 2 years to <18 years, 7 of 10 children with confirmed esophageal candidiasis had successful global response, although two successes subsequently experienced recurrence.[69]

Recommended alternatives for fluconazole-refractory esophageal candidiasis include an echinocandin **(BI*),** amphotericin B **(BI*),** posaconazole **(CII*),** or isavuconazole **(CII*).** Randomized clinical trials in adults with HIV have demonstrated good treatment response when using an echinocandin for esophageal candidiasis, but relapse is more frequent, particularly for OPC. Caspofungin demonstrated comparable efficacy to fluconazole for treatment of esophageal candidiasis (81.5% vs. 85.1%, difference −3.6 [95% CI, −14.7 to 7.5]).[70-73] However, caspofungin efficacy against OPC was numerically lower but not statistically significant (71.4% vs. 83.3%, difference −11.9 [95% CI, −26.8 to 3.0]), while OPC relapse was more frequent with caspofungin at 14 days post-treatment (42.5% vs. 13.2%, difference 29.3% [95% CI, 11.5–47.1] and 28 days post-treatment (59.0% vs. 35.3%, difference 23.7% [95% CI, 3.4–43.9]).[74] Micafungin demonstrated non-inferior efficacy by overall therapeutic cure (both clinical and endoscopic cure) compared to fluconazole for treatment of esophageal candidiasis (85.8% vs. 85.3%, difference 0.5% [95% CI, −5.6 to 6.6]).[75-77] Although micafungin efficacy at end of treatment was comparable to fluconazole for OPC treatment (83.5% vs. 82.1%), symptomatic relapse at 2 weeks post-treatment was more common in micafungin-treated participants than fluconazole-treated participants (32.3%, 18.1%, difference 14.2% [95% CI, 5.6–22.8]).[75,76] Anidulafungin demonstrated similar endoscopic success (cure or improvement) when compared to fluconazole (97.4% vs. 98.7%, difference −1.3% [95% CI, −3.8 to 1.2]) as well as clinical success (cure or improvement in clinical symptoms) (99.1% vs. 99.6%) at the end of therapy.[78-80] However, endoscopically confirmed relapses 2 weeks after end of therapy were more common in the anidulafungin group (53.3% vs. 19.3%, difference 34.0%, [95% CI, 25.8–42.3]). Pediatric bridging studies evaluating echinocandin pharmacokinetics (PK) and safety have determined appropriate dosing of echinocandins and support their good safety profile at these doses. Amphotericin B has historically been used in treatment of esophageal candidiasis with efficacy as a comparator in adult randomized controlled trials (RCTs) of esophageal candidiasis;

however, toxicities are frequent.[71,73,81] Posaconazole has limited efficacy data for treatment of esophageal candidiasis,[62] but newer formulations provide IV and oral options with more stable PK and generally good safety profiles.[64] Isavuconazole (in the form of isavuconazonium sulfate) has promising Phase 2 efficacy and safety data for treatment of uncomplicated esophageal candidiasis in adults with bridging pharmacokinetic data of IV and oral options in children.[82,83]

Invasive Candidiasis

The treatment of choice for invasive disease in children with HIV depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). RCTs in adults without HIV have demonstrated that an echinocandin used to treat candidemia and/or invasive candidiasis had similar efficacy compared to amphotericin B by favorable outcomes at the end of IV therapy (caspofungin 74.3%, amphotericin B 67.8%, difference 7.5% [95% CI, –5.4 to 20.3]; overall study mortality, caspofungin 33.0%, amphotericin B 30.4%); similar efficacy compared across echinocandins (micafungin 70.7%, caspofungin 63.3%, difference 7.4% [95% CI, –2.0 to 16.3][84-88]; overall study mortality micafungin 29.0%, caspofungin 26.4%); and superior efficacy compared to fluconazole (anidulafungin 75.6%, fluconazole 60.2%, difference 15.4 [95% CI, 3.9–27.0]; overall study mortality, anidulafungin 22.8%, fluconazole 31.4%). In a pediatric multicenter, prospective open-label study of caspofungin, 30 of 37 participants with invasive candidiasis and one of one participant with esophageal candidiasis had a successful clinical and microbiological response at the end of therapy.[89] In a pediatric multicenter, prospective observational cohort study of treatment for invasive candidiasis in 541 children without HIV, initial directed therapy with an echinocandin (compared with an azole or amphotericin B) was associated with reduced treatment failure at 14 days (unadjusted, echinocandin 9.8%, azole/amphotericin B 13.1%; adjusted risk difference –7.1% [95% CI, –13.1 to –2.4]) but not at 30 days (adjusted risk difference –0.4% [95% CI, –7.5 to 6.7]).[13]

An echinocandin is recommended for moderately severe to severely ill children with candidiasis because of the fungicidal nature of these agents, as well as the lack of AEs. Fluconazole is a reasonable alternative for people who are less critically ill and who have no recent azole exposure **(AI*).** Voriconazole can be used in situations in which mold coverage is also warranted **(BI*).**[90] Although isavuconazole has activity against *Candida,* a Phase 3, randomized, double-blind, multinational clinical trial for the primary treatment of adults with candidemia or invasive candidiasis failed to demonstrate isavuconazole non-inferiority versus caspofungin (overall response at end IV therapy 60.3% vs. 71.1%, adjusted difference –10.8 [95% CI, –19.9 to 1.8]). Secondary endpoints of all-cause mortality and safety were similar across arms, and median times to bloodstream clearance was comparable.[91]

For infections with *C. glabrata*, an echinocandin is recommended because of the increasing resistance seen against fluconazole for this species **(AII).**[92] Despite this recommendation, clinicians should be aware of the increasing frequency of *C. glabrata* echinocandin resistance. For those 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 intrinsic resistance to fluconazole. For infection with *C. parapsilosis*, fluconazole or amphotericin B is recommended **(BII*).** Previous data suggested a decreased response of *C. parapsilosis* isolates to echinocandins.[84,86,87,93] However, subsequent adult comparative effectiveness data reveal that initial therapy with an echinocandin for *C. parapsilosis* did not result in worse outcomes.[94] Thus, if a person is receiving empirical therapy with an echinocandin and showing clinical improvement when culture of *C. parapsilosis* returns, continuing with this therapy is reasonable. For infections with *C. auris*, an echinocandin is recommended **(AII*),** but clinicians

should check available data on their local susceptibility patterns. Azole resistance is high and amphotericin B resistance is common, but susceptibilities are variable by clade and geographical distribution.[21] *C. auris* resistance to echinocandins is increasing, and pan-resistant *C. auris* has been reported.[21-23]

For many of these clinical scenarios, amphotericin B is an effective but less attractive alternative given concerns for therapy-related toxicity **(BI*).**[84,85,95] Amphotericin B lipid formulations are 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 **(AI).**[96-98] However, amphotericin B deoxycholate is acceptable if a lipid formulation is unavailable or infeasible **(BI*).**

Regardless of the antifungal agent chosen, the recommended duration of therapy for candidemia should be treated for ≥ 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 **(AIII).** 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 a pediatric infectious diseases specialist.

For CNS candidiasis, initial treatment should use amphotericin B **(AIII).**[33,34] Recommended initial treatment in neonates is amphotericin B deoxycholate 1 mg/kg IV daily or liposomal amphotericin B 5 mg/kg IV daily **(BIII).** Addition of flucytosine 25 mg/kg four times daily may be considered as salvage therapy for neonates who have not responded clinically to initial amphotericin B deoxycholate, but toxicities are common. CNS disease in the neonate typically manifests as a meningoencephalitis. Although all amphotericin B formulations penetrate the CNS and have fungicidal activity in the CNS, amphotericin B deoxycholate and liposomal amphotericin B had the highest drug exposures and greatest antifungal efficacy in a rabbit model of hematogenous *C. albicans* meningoencephalitis.[34,99] A comparative effectiveness study found higher mortality in infants treated with lipid formulations of amphotericin B than with amphotericin B deoxycholate or fluconazole.[34,100] However, the study had heterogeneity among the lipid formulations used and institutional care practices, and some institutions have subsequently reported successful outcomes with liposomal amphotericin B in neonates. Lipid formulations may not adequately penetrate the kidneys and thus should only be used with caution in neonates when urinary tract involvement is suspected or confirmed. In a prospective observational study evaluating treatment outcomes of CNS candidiasis in neonates, median time to clear the cerebrospinal fluid (CSF) was longer for infants who received flucytosine plus amphotericin B deoxycholate compared with amphotericin B deoxycholate alone.[34,101] Further, flucytosine is poorly tolerated in neonates, and gastrointestinal toxicity may hinder oral feeding. Micafungin 10 to 15 mg/kg/dose IV daily may be considered in neonates with CNS candidiasis as alternative therapy in special circumstances, such as salvage therapy or situations in which toxicity or drug resistance (e.g., *C. glabrata*) preclude the use of the preferred agents. Beyond the neonatal/infant period, liposomal amphotericin B 5 mg/kg IV daily is recommended with or without flucytosine **(AIII),** although doses up to 10 mg/kg IV daily have been used in non-candidal CNS mycoses with associated higher toxicities. After the patient has responded to initial treatment, fluconazole 12 mg/kg daily may be considered for isolates susceptible to fluconazole. (See the Pharmacokinetics and Dosing of Antifungal Agents section below for characteristics of various antifungal agents.)[102-104] Therapy should be continued for at least one month until all signs, symptoms, and CSF and radiological abnormalities have resolved.[34,105] Infected CNS devices, including ventriculostomy drains and shunts, should be removed if possible **(AIII).** For ocular candidiasis (e.g., endophthalmitis), systemic fluconazole or voriconazole provide most optimal intraocular drug concentrations, while systemic liposomal amphotericin B may be an

alternative, especially when resistant to other antifungal agents. The roles of intravitreal antifungal therapy or vitrectomy should be evaluated jointly on a case-by-case basis by infectious diseases physicians and ophthalmologists.[28,33,34] If a child with uncomplicated invasive candidiasis 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 can be considered when the patient has shown clinical improvement, isolates susceptible to the oral agent, and negative repeat blood cultures following initiation of antifungal therapy **(BII*).**[103,104,106,107] 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*). Decisions to step down to an oral agent should also be guided by considerations of the site of infection and antifungal pharmacokinetics, such as bioavailability and penetration into the target tissues.

Finally, in children who have a central venous catheter in place at the time of candidemia onset, the central line should always be removed when feasible **(AII*).**[7,108] 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.[94] Additionally, an individual patient-level quantitative review of seven randomized trials of adults with candidemia and found that central line removal provided a protective effect against mortality (odds ratio [OR] 0.50; 95% CI, 0.35–0.72).[93] *Candida* infections tend to generate biofilm formation in indwelling catheters or implanted devices, such as prosthetic heart valves.[109] Biofilms are generally resistant to intravenous antifungals. Neglecting to remove catheters increases the chances of treatment failure and/or disease recurrence. Therefore, it is reasonable to conclude that a central venous catheter should be removed when feasible.

Pharmacokinetics and Dosing of Antifungal Agents

Azoles

Fluconazole PK vary significantly with age, and fluconazole is rapidly cleared in children. Daily fluconazole dosing for invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease, with many experts suggesting a loading dose of fluconazole 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 (see Drug Dosing Table).[110] Therapeutic drug monitoring (TDM) should be considered routinely for prevention and management of invasive candidiasis when using itraconazole, voriconazole, posaconazole (esp. for oral suspension, consider for other formulations), or flucytosine.[33,111] TDM should also be considered (by drug and clinical scenario) in populations at risk of extremely low or high drug exposures (e.g., premature neonates, critically ill patients with altered volume of distribution or extracorporeal circuits, altered protein binding [e.g., severe hypoalbuminemia], gastrointestinal absorption problems, drug–drug interactions, or extremes of weight [e.g., morbid obesity or severe acute malnutrition]) or in patients experiencing treatment failure.[33,111] (Note that recommended TDM targets and timing are typically based on adult data and may be derived from non-candidal fungal infections.)

Itraconazole oral solution bioavailability is lower in children than in adults (see Drug Dosing Table).[60,112] Administrating itraconazole oral solution on an empty stomach improves absorption (in contrast to the capsule formulation, which is best administered under fed and acidic conditions), and

monitoring itraconazole serum concentrations, like most azole antifungals, is key in management (generally itraconazole trough levels [timing: approximately 5–7 days with loading dose, 10–14 days without loading dose] should be ≥0.5 µg/mL [prophylaxis] or ≥1 µg/mL [treatment]; trough levels >3 µg/mL to 4 µg/mL may be associated with increased toxicity).[111] Super-bioavailability itraconazole (SUBA-itraconazole) is approved by the U.S. Food and Drug Administration (FDA) in adults only; therefore, no pediatric dosing is available.[113-117]

Voriconazole has considerable experience in children, including for treatment of esophageal candidiasis and candidemia.[6,49,118,119] 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. 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 (see Drug Dosing Table).[118-120] In addition, therapeutic trough (timing: 2–5 days [approximately 2 days with loading dose, approximately 5 days without loading dose]) voriconazole drug levels (generally thought to be ≥0.5 µg/mL [prophylaxis] or ≥1 µg/mL to 2 µg/mL [treatment]; toxicity ceiling 4 to 5.5 µg/mL) should be monitored because of significant interindividual variability in voriconazole PK in children with invasive fungal infection.[111,121] For example, voriconazole clearance depends on allelic polymorphisms of cytochrome P450 (CYP) CYP2C19, resulting in poor and extensive metabolizers of voriconazole.[122,123] It is estimated that 20% of Asian and 3% to 5% of White populations are poor metabolizers of voriconazole, further underscoring the importance of monitoring voriconazole levels to ensure proper dosing.[122]

Posaconazole is available in four formulations for use in children.[64] **Note that the various formulations are not substitutable and have differences in dosing.** The original posaconazole *oral suspension* is FDA approved in people aged ≥13 years.[124] Effective absorption of the posaconazole oral suspension strongly requires taking the medication with food, ideally a high-fat meal (or liquid nutritional supplement or acidic carbonated beverage in people who cannot eat a full meal); taking posaconazole oral suspension on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The exact pediatric dosing for posaconazole oral suspension 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. In adults, 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 people who are severely ill because of findings of a marginal increase in exposure with more frequent dosing (see Drug Dosing Table). Posaconazole *delayed-release tablets* are approved in children ≥2 years who weigh >40 kg. The posaconazole delayed-release tablet formulation has better absorption given its delayed release in the small intestine, but absorption will still be slightly increased with food. If the person is unable to take food, the tablet is recommended; but tablets are to be swallowed whole, not divided, crushed, or chewed—although a case series of 10 encounters using crushed delayed-release tablets in nine children achieved target posaconazole concentrations in 90% of encounters.[125] There is potential for overdosing if this tablet formulation is dosed inappropriately.[126,127] The posaconazole *PowderMix for delayed-release oral suspension* is approved in children aged ≥2 years who weigh ≤40 kg; note that the recommended dosage cannot be achieved with this formulation in children >40 kg.[124] Posaconazole PowderMix for delayed-release oral suspension should be administered with food and using the copackaged notched tip syringe. The posaconazole *injection* is approved in children aged ≥2 years. Posaconazole *injection* must be administered through an in-line filter by slow intravenous infusion, not as a bolus injection (see FDA package insert for details).[64] For all formulations, posaconazole target trough (timing: 5 days with a loading dose, 7 days without a loading dose) levels

for prophylaxis are ≥0.5 µg/mL to 0.7 µg/mL with treatment targets ≥1 µg/mL to 1.5 µg/mL; the trough toxicity ceiling is >3 µg/mL to 3.75 µg/mL.[111]

Isavuconazole is a new triazole that was FDA approved in 2015 for treatment of invasive aspergillosis and invasive mucormycosis with both oral (capsules only) and IV formulations. Isavuconazole has activity against *Candida*.[91] Isavuconazole is available for administration in its prodrug form isavuconazole sulfate. In adults, isavuconazonium sulfate has a mean plasma half-life of 130 hours after IV administration; the oral capsule has an absolute bioavailability of 98%.[128] As of December 2023, isavuconazonium sulfate (prodrug of isavuconazole) *injection* is FDA approved in children ≥1 year old, and isavuconazonium sulfate *capsules* are approved in children ≥6 years old who weigh ≥16 kg (see Drug Dosing Table). The FDA approval is based on a Phase 1 pediatric safety, tolerability, and PK study[83] and a Phase 2 open-label, noncomparative, multicenter study for treatment of invasive aspergillosis or invasive mucormycosis in 31 children aged 1 to 17 years who experienced 6.5 % (95% CI, 0.79–21.42) all-cause mortality through 42 days.[129]

Echinocandins

Data from studies using echinocandins (caspofungin, micafungin, and anidulafungin) are sufficient to recommend these agents as alternatives to fluconazole for esophageal candidiasis **(BI*)** and as first-line therapy for invasive candidiasis **(AI*).**[13,88,89,95,130-141]

Echinocandins are generally not recommended for treatment of CNS *Candida* infections due to concerns that these agents penetrate CSF poorly. However, some research has evaluated the potential of echinocandins for neonatal hematogenous *Candida* meningoencephalitis. A nonneutropenic rabbit model of neonatal hematogenous *Candida* meningoencephalitis found untreated *Candida albicans* infection burdens in CSF cultures beneath the limit of quantification, despite the presence of established infection in various other CNS subcompartments (e.g., cerebrum, cerebellum, spinal cord, and meninges), and micafungin penetrated most CNS compartments (highest concentrations in meninges and choroid, not reliably detected in CSF) when dosed sufficiently.[142] Micafungin doses ≥10 mg/kg/dose once daily (with safety data supporting up to 15 mg/kg/day) may be necessary for the treatment of candidemia with meningoencephalitis.[137,138,142,143] Population pharmacokinetics and modeling of micafungin in 47 infants with proven or presumptive disseminated candidiasis indicated that a dose of 10 mg/kg/dose daily resulted in 83% of infants with micafungin areas under the concentration-time curve (AUC) that are associated with near-maximal decline in fungal burden within the CNS.[138] An RCT evaluating micafungin 10 mg/kg/dose daily versus amphotericin B in infants <4 months with suspected or proven *Candida* meningoencephalitis was terminated early (due to slow recruitment) with only 30 participants enrolled (20 allocated to micafungin, 10 amphotericin B), which was 13% of the targeted enrollment. Prior to study termination, fungal-free survival at 1 week after end of therapy was 60% for micafungin versus 70% for amphotericin B with all-cause mortality 15% (micafungin) versus 10% (amphotericin B).[144]

A PK study of caspofungin in immunocompromised children with HIV 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.[132] Significantly higher doses of caspofungin have been studied in adults 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. A multicenter RCT of infants <3 months old with invasive candidiasis with allocation to caspofungin 2 mg/kg/dose IV daily (equivalent to median dose of 25 mg/m^2/day) versus amphotericin B deoxycholate

1 mg/kg/dose IV daily was terminated early for low enrollment.[145,146] In the full-analysis-set population, fungal-free survival in at 2 weeks after treatment was similar across arms (71.0% versus 68.8%; difference, stratified by weight, –0.9% [95% CI, –24.3% to 27.7%]), with a smaller proportion of AEs in the caspofungin arm.

The recommended dose of micafungin for children aged 2 years to 17 years is 2 to 4 mg/kg/dose daily, but neonates require doses of micafungin 10 to 15 mg/kg/dose daily and infants <15 kg may benefit from 5 to 7 mg/kg/dose daily (see Drug Dosing Table below for recommended dosing according to age/weight bands).[88,95,135-137,147,148] Micafungin demonstrates dose-proportional PK, and an inverse relationship between age and clearance, suggesting a need for increased dosage in young children.[138] Clearance of the drug in neonates was more than double that in older children and adults.[139] Dosages of micafungin at least 10 mg/kg/day are recommended in premature neonates. Doses of 10 mg/kg/day results in AUC values consistent with an adult dosage of micafungin 100 to 150 mg/day; safety data from clinical studies at doses of 10 to 15 mg/kg daily for infants <4 months old did not reveal new safety signals.[105,136-138]

In 2020, the FDA approved anidulafungin for treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in children aged 1 month and older (see Drug Dosing Table). Although dosing in adults differs by treatment indication for candidemia (200-mg load, then 100 mg once daily thereafter) versus esophageal candidiasis (100-mg load, then 50 mg once daily thereafter), a separate pediatric dosing for esophageal candidiasis is not FDA approved.[80] One PK study of anidulafungin in 25 neutropenic children without HIV 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 daily and 100 mg daily, respectively.[140] A PK study of 15 neonates and infants indicated that neonates and infants receiving 1.5 mg/kg/day of anidulafungin have exposures similar to children receiving similar weight-based dosing and adults receiving 100 mg/day.[149] 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 daily of anidulafungin was successful in treating the infection.[141] In a prospective, open-label noncomparative, multicenter, international study to evaluate safety, efficacy, and PK of anidulafungin for treatment of invasive candidiasis, 49 participants aged 2 years to <18 years receiving anidulafungin (3 mg/kg Day 1, 1.5 mg/kg daily thereafter for 10–35 days, followed by optional fluconazole) had 8.2% probability of all-cause mortality (4/49) by end of IV therapy and 14.3% (7/49) by Week 6 follow-up. No deaths were considered treatment related, and global response was 70.8% at end of IV therapy.[150] Under the same protocol, 19 participants aged 1 month to <2 years received anidulafungin for 5 to 25 days; PK were similar to adult participants, and global success was 68.8% at end of IV therapy.[150] Rezafungin is approved in adults only; therefore, no pediatric dosing is available.[151]

Polyenes

Conventional amphotericin B (sodium deoxycholate complex, AmB-D) 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 **(CIII).**[152-154] 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 AmB-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 with rapid tissue penetration.[155,156] 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.[157] 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 for candidiasis. 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.[158] 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.[49] Flucytosine has been used in combination with amphotericin B in some children with severe invasive candidiasis, particularly in those with CNS 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 **(CIII).**[159,160]

For a summary of fungal species, antifungal drugs, activity, route, clearance, CSF penetration, drug monitoring targets, and AEs, refer to the *American Academy of Pediatrics Red Book 2024–2027* chapter on Antifungal Drugs for Systemic Fungal Infections.

Monitoring Response to Therapy and Adverse Events, Including IRIS

All medications, including antifungals and antiretrovirals, should be checked for contraindications, warnings, precautions, and administration instructions prior to prescribing, particularly for newer drugs and formulations. For example, administration of the posaconazole PowderMix formulation with alcohol is not recommended, and posaconazole PowderMix and anidulafungin are contraindicated in individuals with known or suspected hereditary fructose intolerance (see corresponding FDA label).

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.

Azoles

The azole drugs have relatively low toxicity, but because of their ability to inhibit the CYP-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. Potential azole-related drug–drug interactions are pertinent to certain drugs from many ARV classes, including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, an integrase strand transferase inhibitor (i.e., elvitegravir), a CCR5 antagonist (i.e., maraviroc), and pharmacokinetic boosting agents (e.g., ritonavir or cobicistat). Most nucleos(t)ide reverse transcriptase inhibitors in current use have no major drug–drug interactions, but itraconazole may increase exposures and AEs from tenofovir disoproxil fumarate and tenofovir alafenamide. Most integrase strand transferase inhibitors (i.e., dolutegravir, bictegravir, raltegravir, cabotegravir) do not require dose adjustments with most azoles, but elvitegravir has drug–drug interactions with many azoles. Lenacapavir has possible drug–drug interactions with many azoles, but no dose adjustments are recommended. The potential for drug–drug interactions should be carefully evaluated before initiation of therapy **(AII*).**[161]

TDM should be used to optimize management of itraconazole, voriconazole, and posaconazole. The benefits of TDM are likely greatest in treatment of severe disease, such as invasive candidiasis, but TDM may be considered in other circumstances for ensuring appropriate azole exposures to improve effectiveness and/or decrease toxicity. Generally, itraconazole trough levels ≥0.5 µg/mL (prophylaxis) or ≥1 µg/mL (treatment) are ideal, and trough levels >3 to 4 µg/mL may be associated with increased toxicity. Target voriconazole trough levels are ≥0.5 µg/mL for prophylaxis and ≥1 µg/mL to 2 µg/mL for treatment, with a trough toxicity ceiling of 4 to 5.5 µg/mL. Posaconazole target trough levels for prophylaxis are ≥0.5 µg/mL to 0.7 µg/mL with treatment targets ≥1 µg/mL to 1.5 µg/mL; the trough toxicity ceiling is >3 µg/mL to 3.75 µg/mL.[111] Note that these targets are based in large part on adult data from a variety of invasive fungal infections, not necessarily on *Candida* PK/pharmacodynamic targets; for example, voriconazole targets were based primarily on studies of invasive aspergillosis.

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting (10% to 40% of recipients). 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 recipients). 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 people receiving voriconazole.[162] 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.[163] Voriconazole administration has been associated with fluorosis. Voriconazole is a tri-fluorinated agent with up to 16% fluoride and can result in excess fluoride accumulation in the recipient after prolonged exposure. Recipients will often present with non-specific bone pain and have periosteal reaction seen on radiographs.[164] 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.[165,166] Voriconazole should not be administered intravenously to people with renal impairment, including people with creatinine clearance <50 mL/min, or people who require hemodialysis or continuous venovenous hemodiafiltration (see voriconazole's FDA label). This is not due to the drug itself, but because intravenous administration of voriconazole requires coadministration with sulphobutylether-β-cyclodextrin (SBECD) as an excipient. SBECD can accumulate in people with impaired renal function.

Polyenes

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 usually occurs 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.

Echinocandins

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 three participants had AEs potentially related to the drug (hypokalemia in all three children, elevated bilirubin in two children, and decreased hemoglobin and elevated alanine aminotransferase in one child).[132] 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%) participants experienced one or more drug-related clinical AEs, including one patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. One or more drug-related laboratory AEs were reported in two participants, including one patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related AEs in this study were considered serious or led to discontinuation of caspofungin.[132] In a prospective multicenter trial for primary or salvage treatment of *Candida* or *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 AEs occurring in 26.5% and 34.7% of participants, respectively, similar to proportions seen in adults. Drug-related clinical AEs 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 AEs led to therapy interruption or discontinuation.[89]

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 participants who weighed 40 kg, and 100 mg for participants who weighed >40 kg, was well tolerated. AEs were similar for both treatment arms and reflected those experienced by people with comorbid conditions. These AEs included sepsis, fever, vomiting, diarrhea, anemia, thrombocytopenia, and hypokalemia. Participants in the micafungin group experienced significantly fewer AEs 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 participants receiving micafungin experienced serious AEs, including a worsening of renal failure, a preexisting condition, and a moderate increase in serum creatinine resulting in discontinuation of therapy. Participants 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.[95]

A multicenter, ascending-dosage study of anidulafungin in 25 children with neutropenia, without HIV and aged 2 years to 17 years, showed anidulafungin to be well tolerated and observed no drug-related serious AEs. 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.[140] In a prospective, open-label, noncomparative, multicenter international study of participants aged 2 years to <18 years old receiving anidulafungin followed by optional fluconazole, the most common treatment-emergent AEs (>10%) were vomiting, diarrhea, pyrexia, epistaxis, headache, abdominal pain, alanine transaminase (ALT) increased, and hypotension. Most were mild or moderate in severity, but five severe AEs occurred in one patient each: neutropenia, gastrointestinal hemorrhage, increased transaminases, hyponatremia, and myalgia. Five participants (10.2%) discontinued treatment due to AEs, and AEs were considered related to anidulafungin in four participants (increased transaminases in two cases, vomiting, generalized pruritis); two participants (4.1%) underwent infusion rate reduction or temporary discontinuation due to AEs. Serious AEs were observed in 23 participants (46.9%) with two reported as related to anidulafungin (increased transaminases and gastrointestinal hemorrhage).[167] Under the same protocol, in 19 participants aged 1 month to <2 years, the most frequent treatment-emergent AEs (>10%) were anemia, diarrhea, pyrexia, vomiting, increased ALT, increased aspartate transaminase, bacteremia, pancytopenia, rash, sepsis, and thrombocytopenia. Most treatment-emergent AEs were mild to moderate with 10 severe treatment-emergent AEs in 7 (36.8%) participants. Five AEs were considered serious (abdominal sepsis, coagulopathy, diarrhea, pancytopenia, and urinary tract infection), of which one event of diarrhea was considered related to anidulafungin and led to discontinuation.[150]

Immune reconstitution inflammatory response syndrome (IRIS) associated with *Candida* infection has not been described in children with HIV. However, evidence suggests that candidiasis (other than *Candida* esophagitis) occurs with increased frequency in adults during the first 2 months after initiation of ART.[168]

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 **(AI*).**[59,60,68]

Approximately 50% to 60% of people with fluconazole-refractory OPC and 80% of people with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution.[65,67,68,169,170] Therefore, itraconazole solution is recommended to treat fluconazole-refractory OPC and fluconazole-refractory esophageal candidiasis **(AI*).** Posaconazole is a second-generation orally bioavailable triazole that has been effective in adolescents and adults with HIV who have azole-refractory OPC or esophageal candidiasis.[62] Although experience in children is still limited, newer posaconazole formulations provide more consistent absorption and drug exposures or the option of IV therapy. Thus, posaconazole is recommended for OPC in children with fluconazole-refractory disease **(AI*).**[61-63,171] Similarly, voriconazole has supporting RCT data in immunocompromised adults (most with HIV) demonstrating that voriconazole is at least as effective as fluconazole in treatment of biopsy-proven esophageal candidiasis, but AEs with voriconazole were more frequent.[66] Given supporting pediatric PK and dosing data, as well as efficacy data in a limited number of immunocompromised children, voriconazole may also be considered for treatment of esophageal candidiasis in fluconazole-refractory disease **(AI*).**[69] Randomized clinical trials in adults with HIV have demonstrated good treatment response when using an echinocandin for esophageal candidiasis, but relapse is more frequent, particularly for OPC.[70,72,75,76,172] Pediatric studies evaluating echinocandin PK and safety have determined appropriate dosing of echinocandins and support their good safety profile at these doses. Thus, echinocandins may be considered alternative treatment options when IV therapy is necessary for azole-refractory esophageal candidiasis and possibly for azole-refractory OPC **(BI*).**

Amphotericin B has historically been used in treatment of esophageal candidiasis with efficacy as a comparator in adult RCTs of esophageal candidiasis, but toxicities are frequent. Thus, amphotericin B is recommended as an alternative agent for esophageal candidiasis **(BI*).**[71,73,81] An amphotericin B dose of 1 mL given orally four times daily of a 100-mg/mL suspension sometimes has been effective in people with OPC who do not respond to itraconazole solution; however, this product is not commercially available in the United States and requires compounding by pharmacies **(CIII).**[68,173,174] Lipid formulations of amphotericin B IV may be considered if needed.[175] Although lower dosing for pediatric OPC or esophageal candidiasis has not been established, the recommended adult dosing range of 3 to 4 mg/kg/day would fall within the standard pediatric dosing range. Low-dose IV amphotericin B (0.3–0.5 mg/kg/day) has been effective and may be considered in children with refractory OPC or esophageal candidiasis **(BII*),**[49,68,81,176] while some adult sources recommend a dose of 0.3 mg/kg/day for OPC and dosing of 0.3 to 0.7 mg/kg/day for esophageal candidiasis.[34,175]

Posaconazole may also be considered as a possible alternative for fluconazole- or itraconazole-refractory esophageal candidiasis **(CII*).**[62,177] Isavuconazole is another alternative treatment due to promising Phase 2 efficacy and safety data for treatment of uncomplicated esophageal candidiasis in adults with bridging pharmacokinetic data of IV and oral options in children **(CII*).**[82,83]

Invasive Disease

As noted above, the treatment of choice for invasive disease in children with HIV 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; however, there is extensive clinical experience with echinocandins in children. Invasive candidiasis associated with neutropenia in people undergoing hematopoietic stem cell 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 **(AI*).**

Various amphotericin B formulations exist for management of refractory disease. Lipid amphotericin B formulations appear to be at least as effective as conventional amphotericin B for treating serious fungal infections,[178,179] and one efficacy trial including 98 children in the modified intention-to-treat analysis had comparable treatment success between liposomal amphotericin B (76.0%) and micafungin (72.9%), although participants with liposomal amphotericin B (16.7%) had more AEs leading to treatment discontinuation than micafungin (3.8%).[95,175] Further, the lipid formulations have less acute and chronic toxicity. An RCT of 702 participants, including 75 children aged 2 through 12 years, compared liposomal amphotericin B versus conventional amphotericin for empirical therapy in participants with persistent febrile neutropenia. Liposomal amphotericin B demonstrated similar efficacy but fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity.[96] Thus, lipid formulations of amphotericin B are preferred over amphotericin B deoxycholate, although amphotericin B deoxycholate is an acceptable alternative when a lipid formulation is not available **(AI).** Two lipid formulations are used: ABLC and liposomal amphotericin B lipid complex.[96,180,181]

For invasive candidiasis, ABLC is administered as 5 mg/kg body weight IV once daily over 2 hours.[96,180,182] 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 (1) treatment of recurrence is typically effective; (2) there are risks of compounding toxicities; (3) the potential exists for development of resistance; (4) there are concerns for drug–drug interactions; (5) additional chronic medications may add to ART adherence challenges; and (6) prophylaxis can prove costly **(AII*).** Although similar considerations apply to esophageal candidiasis, providers should weigh that esophageal disease typically causes more significant morbidity and is associated with more severe immune suppression. In all cases of candidiasis in children living with HIV, immune reconstitution with ART children should be a priority. Indeed, all infants and children with HIV should be initiated on ART, particularly those who develop candidiasis (**AI** for children aged <3 months, **AI*** for older children).[183-185] See the Pediatric Antiretroviral Guidelines for more information. However, when recurrences are frequent and severe despite ART, secondary prophylaxis may be considered on a case-by-case scenario.[57,186-192] Data from studies of adults with HIV on ART suggest that suppressive therapy with systemic azoles, either with oral fluconazole, considered first-line therapy **(AI*),** or itraconazole solution, voriconazole, or posaconazole as alternatives **(BII*),** can be effective and may be considered.[59,66,177,190,193]

Experience with adults with HIV suggests that in children or adolescents 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 and may be considered **(BII*).**

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 and other

OIs, discontinuation of secondary prophylaxis can be considered when a patient's CD4 count or percentage has risen to CDC HIV stage 2 (moderate immunosuppression) or 1 (no or mild immunosuppression) with evidence of immune reconstitution **(BII*).**[194-198] HIV infection staging (see HIV Infection Staging Table for more information) classifies severity of HIV disease primarily according to CD4 cell count (or CD4 percentage, if CD4 cell count is missing), age (as CD4 norms vary by age), and other clinical factors (e.g., acute/early HIV or most AIDS-defining OIs).

Dosing Recommendations for Prevention and Treatment of Candidiasis

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 despite ART. • Fluconazole 6 mg/kg body weight (maximum 200 mg/dose) PO three times weekly	• Fluconazole 3–6 mg/kg body weight PO daily (maximum 200 mg/day) • Itraconazole oral solution, 2.5 mg/kg body weight/dose PO twice daily	Secondary Prophylaxis Indicated (Limited Data in Children) • Frequent or severe recurrences despite ART • In patients with initial fluconazole-refractory OPC or esophageal candidiasis that subsequently responded to voriconazole, posaconazole, or an echinocandin, may consider continuation of the effective drug until immune reconstitution Criteria for Discontinuing Secondary Prophylaxis • When CD4 count or percentage has risen to HIV stage 1 or 2. See HIV Infection Stage Table for more infection. Criteria for Restarting Secondary Prophylaxis • Frequent severe recurrences
Treatment	Oropharyngeal *Uncomplicated Infection* • Clotrimazole troches, 10-mg troche PO four or five times daily	Oropharyngeal (Fluconazole-Refractory) • Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily (maximum 200–400 mg/day) for 7–14 days	Itraconazole oral solution **should not** be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease.

	• Nystatin suspension 4–6 mL PO four times daily, *or* one or two 200,000-unit flavored pastilles by mouth four or five times daily *Moderate to Severe OPC* • Fluconazole 3–6 mg/kg/dose PO once daily (maximum dose: 400 mg/day) *Treatment Duration* • 7 to 14 days	• Posaconazole PowderMix for delayed-release oral suspension in children age ≥2 years and in the weight band for 7–14 days: o *10 kg to <12 kg*: 90 mg PO twice daily on Day 1, followed by 90 mg PO once daily o *12 kg to <17 kg:* 120 mg PO twice daily on Day 1, followed by 120 mg PO once daily o *17 kg to <21 kg:* 150 mg PO twice daily on Day 1, followed by 150 mg PO once daily o *21 kg to <26 kg:* 180 mg PO twice daily on Day 1, followed by 180 mg PO once daily o *26 kg to <36 kg:* 210 mg PO twice daily on Day 1, followed by 210 mg PO once daily o *36–40 kg:* 240 mg PO twice daily on Day 1, followed by 240 mg PO once daily • Posaconazole delayed-release *tablets* in children ≥2 years old and >40 kg body weight: 300 mg PO twice daily on Day 1, followed by 300 mg PO once daily for 7–14 days • Posaconazole oral suspension: 6 mg/kg/dose three times daily for 7–14 days • Posaconazole IV: 6 mg/kg/dose (maximum 300 mg) IV twice daily on Day 1, followed by 6 mg/kg/dose (maximum 300 mg) IV once daily for 7–14 days • *Alternative:* Voriconazole: Dosing as per esophageal disease below • *Alternative:* Echinocandins: Dosing as per esophageal disease below • *Alternative:* Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established.	Fluconazole Dosing Considerations 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.

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		• *Alternative:* Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily	
	Esophageal Disease • Fluconazole 6 mg/kg/day PO once on Day 1, then 3-6 mg/kg/dose PO once daily (maximum dose: 12 mg/kg/day, 400 mg/day) *Treatment Duration* • 14–21 days	Esophageal Disease (Intolerance of Oral Therapy) • Fluconazole 6 mg/kg/day IV once on Day 1, then 3–6 mg/kg/dose IV once daily (maximum dose: 12 mg/kg/day, 400 mg/day) for 14–21 days *Echinocandins* • Anidulafungin o *Aged 1 Month–17 Years*: Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV (maximum 100 mg/day) • Caspofungin o Infants Aged <*3 Months*: 25 mg/m^2 BSA/dose daily IV o *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. • Micafungin 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). o *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. o *Ages ≥4 Months and Weight ≤30 kg:* 3 mg/kg body weight/dose IV daily	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		○ *Ages ≥4 Months and Weight >30 kg:* 2.5 mg/kg body weight/dose IV daily (maximum dose: 150 mg/day) • Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established. • Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily Esophageal Disease (Fluconazole-Refractory) • Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily • Voriconazole ○ *Ages 2 Years to <12 Years:* 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. ○ *Ages 12–14 Years and Weight <50 kg:* 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. ○ *Ages 12–14 Years and Weight ≥50 kg:* 200 mg PO/IV every 12 hours ○ *Ages ≥15 Years and Weight <40 kg:* 100 mg PO/IV every 12 hours ○ *Ages ≥15 Years and Weight ≥40 kg:* 200 mg PO/IV every 12 hours • *Alternative:* Echinocandins: Dosing as above	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		• *Alternative:* Lipid formulation amphotericin B: Dosing as above • *Alternative:* Amphotericin B (deoxycholate): Dosing as above • *Alternative:* Posaconazole: Dosing as above • *Alternative:* Isavuconazonium sulfate IV (372 mg/vial) o *Ages 1 Year to <3 Years and Weight <18 kg:* 15 mg/kg body weight/dose every 8 hours IV loading for six doses (48 hours), followed by 15 mg/kg once daily o *Ages 3 Years to <18 Years and Weight <37 kg:* 10 mg/kg every 8 hours IV loading for 6 doses (48 hours), followed by 10 mg/kg once daily IV o *Ages 3 Years to <18 Years and Weight ≥37 kg:* 372 mg (total dose) every 8 hours IV loading for 6 doses (48 hours), followed by 372 mg (total dose) once daily IV • *Alternative:* Isavuconazonium sulfate capsules (74.5 mg/capsule) o *Ages 6 Years to <18 Years and Weight 16 kg to <18 kg:* 149 mg (2 capsules) PO every 8 hours loading for six doses (48 hours), followed by 149 mg (2 capsules) PO once daily o *Ages 6 Years to <18 Years and Weight 18 kg to <25 kg:* 223.5 mg (3 capsules) PO every 8 hours loading for 6 doses (48 hours), followed by 223.5 mg (3 capsules) PO once daily	

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Indication	First Choice	Alternative	Comments/Special Issues
		o *Ages 6 Years to <18 Years and Weight 25 kg to <32 kg:* 298 mg (4 capsules) PO every 8 hours loading for six doses (48 hours), followed by 298 mg (4 capsules) PO once daily o *Ages 6 Years to <18 Years and Weight ≥32 kg:* 372 mg (5 capsules) PO every 8 hours loading for six doses (48 hours), followed by 372 mg (5 capsules) PO once daily *Treatment Duration* • 14–21 days	
	Invasive Disease: Moderately Severe to Severely Ill *Echinocandin Recommended* • Anidulafungin o *Aged 1 Month–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 (maximum 100 mg/day) • Caspofungin: o *Infants Aged <3 Months*: 25 mg/m^2 BSA/dose once daily IV o *Aged 3 Months–17 Years:* 70 mg/m^2 BSA/day loading dose followed by 50 mg/m^2 once daily (maximum 70 mg). Note: Dosing of caspofungin in children should be based on body surface area.	Invasive Disease • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight IV/PO once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia) o For infants aged ≤3 months and gestational age <30 weeks, maintenance dosing is 9 mg/kg/dose IV/PO daily • Lipid formulations of amphotericin B, 3–5 mg/kg body weight IV once daily • Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily in the neonatal period • Voriconazole: o *Ages 2 Years to <12 Years:* 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours.	Central venous catheters should be removed, when feasible, in children with HIV with fungemia. The preferred treatment for invasive disease in children with HIV depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). If a child with uncomplicated invasive candidiasis 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 can be considered when the patient is clinically improved, has isolates susceptible to the oral agent, and have negative repeat blood cultures following initiation of antifungal therapy. Voriconazole can be used in situations in which mold coverage is also warranted.

	• Micafungin: 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). o *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. o *Infants <15 kg body weight:* 5–7 mg/kg/day o *Children* ≤40 kg body weight and aged 2–8 years: 3–4 mg/kg body weight/dose daily IV o *Children* ≤40 kg body weight and aged 9–17 years: 2–3 mg/kg body weight/dose daily o *Children* >40 kg body weight: 100 mg/dose daily IV *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture. Invasive Candidiasis: Mildly to Moderately Ill *Fluconazole Recommended* • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 600 mg)	o *Ages 12–14 Years and Weight <50 kg:* 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours. o *Ages 12–14 Years and Weight ≥50 kg:* Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. o *Ages ≥15 Years and Weight <40 kg:* Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 100 mg PO every 12 hours. If response is inadequate, may increase to 150 mg PO every 12 hours. o *Ages ≥15 Years and Weight ≥40 kg:* Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture.	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
	• For infants aged ≤3 months and gestational age <30 weeks, fluconazole maintenance dosing is 9 mg/kg/dose IV daily. • Avoid fluconazole for *C. krusei* and *C. glabrata.* See dosing for echinocandins above. • Use caution with echinocandins for *C. parapsilosis*. *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture.		
	Invasive Disease: CNS *Neonates* • *Initial:* Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily, *or* liposomal amphotericin B 5 mg/kg body weight/dose IV daily • *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily *Children* • *Initial:* Liposomal amphotericin B 5 mg/kg body weight/dose IV daily +/- flucytosine 25 mg/kg body weight/dose PO four times daily	Invasive Disease: CNS *Neonates* • Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily, *or* liposomal amphotericin B 5 mg/kg body weight/dose IV daily, *and* • Flucytosine 25 mg/kg body weight/dose PO four times daily as salvage therapy *Children* • *Initial:* Amphotericin B deoxycholate 0.7–1 mg/kg body weight/dose IV daily IV daily (maximum 1.5 mg/kg/day) +/- flucytosine 25 mg/kg body weight/dose PO four times daily • *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg)	Infected CNS devices should be removed if possible. For patients in whom a ventricular device cannot be removed, amphotericin B deoxycholate could be administered through the device into the ventricle. Intrathecal neonatal doses have ranged from 0.5 mg/day in 2 mL of D5W to 0.6 mg/day in 0.5 mL of D5W (total doses were 0.15 mg to 8.6 mg); doses of 0.125 to 0.25 mg have been administered to children via an Ommaya reservoir. Lipid formulations of amphotericin may not adequately penetrate the kidneys and should only be used with caution in neonates when urinary tract involvement is suspected or confirmed.

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
	• *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg) *Treatment Duration* • ≥1 month until all signs, symptoms, and CSF and radiographic abnormalities have resolved		Fluconazole dosing for CNS candidiasis is unknown but based on dosing for *Candida* invasive disease and maximums from cryptococcal meningitis. In neonates with CNS candidiasis, micafungin 10–15 mg/kg/dose IV daily may be considered as alternative therapy in special circumstances, such as salvage therapy or situations in which toxicity or drug resistance (e.g., *C. glabrata*) preclude the use of the preferred agents.

Key: ART = antiretroviral therapy; BSA = body surface area; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; D5W = 5% dextrose in water; IV = intravenous; OPC = oropharyngeal candidiasis; PK = pharmacokinetic; PO = oral

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Coccidioidomycosis

Updated: June 05, 2025
Reviewed: June 05, 2025

Panel's Recommendations
• Routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended (BIII). • Amphotericin B is recommended as initial therapy for the treatment of diffuse pulmonary or disseminated coccidioidomycosis (in the absence of central nervous system involvement) (AII*). • There is no evidence that lipid preparations of amphotericin B are more effective than amphotericin B deoxycholate for the treatment of coccidioidomycosis in children. Lipid preparations are often preferred because they are better tolerated and associated with less nephrotoxicity than amphotericin B deoxycholate (AII*). • A triazole agent such as fluconazole or itraconazole should be used as consolidation therapy at the completion of amphotericin B therapy (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). • For patients with mild disease (e.g., focal pneumonia), initial therapy with fluconazole or itraconazole is appropriate (AII*). • Itraconazole is preferred for treatment of skeletal infections (AII*). • Voriconazole (as a single agent or in combination with caspofungin), posaconazole, isavuconazole, and amphotericin B have been used as salvage therapy in patients with refractory disease (AII*). • Because absorption varies from patient to patient, serum itraconazole, voriconazole, and posaconazole levels should be measured to ensure effective and nontoxic concentrations, monitor drug levels following changes in dosage, and assess compliance (BIII). • Fluconazole is the preferred agent for treating coccidioidal meningitis (AII*). Intravenous amphotericin B preparations are not preferred for treating coccidioidal meningitis (AII*). Intrathecal, intracisternal, or intraventricular amphotericin B deoxycholate has been used to treat people with refractory disease (AIII). • Lifelong antifungal suppression (secondary prophylaxis) with either fluconazole or itraconazole is recommended for children with HIV after disseminated, diffuse pulmonary, and/or meningeal coccidioidomycosis, even if immune reconstitution is achieved with antiretroviral therapy (AII*). • Lifelong secondary prophylaxis should be considered for children with mild disease and CD4 T lymphocyte (CD4) cell count <250 cells/mm^3 or CD4 percentage <15% (BIII). Despite immune reconstitution, relapse of coccidioidomycosis may occur in children with HIV who initiated secondary prophylaxis due to mild disease and immunosuppression. Therefore, lifelong azole prophylaxis should be considered (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.*

Introduction

Coccidioidomycosis is an endemic mycosis of considerable clinical significance in the Western Hemisphere, including among adults with HIV. Disease syndromes are well-described in adults and immunocompetent children. Because coccidioidomycosis in children with HIV has been significantly less common than in adults, data are limited on specific clinical manifestations and treatment and preventive strategies in this patient population. Therefore, many of our guidelines are based on experience and case reports in adults and limited cases in children without HIV.

Epidemiology

Coccidioidomycosis is caused by the endemic, soil-dwelling dimorphic fungus, *Coccidioides*. Two genetically distinct species, *Coccidioides posadasii* and *C. immitis*, have been identified using molecular and biogeographic characteristics. *C. posadasii* is widely distributed throughout the southwestern United States, northern Mexico, and Central and South America. *C. immitis* is confined mainly to the western United States, with most cases reported in California, Arizona, Utah, and Washington State.[1-3] Clinical illness caused by each species is indistinguishable. Infection usually results from inhalation of spores (arthroconidia) produced by the mycelial form, which grows most readily in arid, windy environments, especially when hot summers are preceded by rainy seasons.[4] Due to projected changes in temperature and precipitation secondary to climate changes, the areas of endemicity are estimated to expand north and farther east and along the Pacific coast.[5,6] Rates of coccidioidomycosis disease have increased significantly in California in recent years, likely associated with climate change. Disease in non-endemic regions is usually the result of reactivation of a previous infection or from infection acquired during travel to an endemic region.[7,8] Contaminated fomites such as dusty clothing or agricultural products have been implicated as rare sources of infection.[9,10]

Most cases of coccidioidomycosis are caused by primary infection. Incidence is influenced by both conducive environmental conditions and activities that predispose people to the inhalation of spores. Increased infection rates have been attributed to population shifts to endemic regions, climatic conditions, construction,[11] dust storms, and better recognition of disease manifestations.[5,12] Surveillance in California revealed an increase in pediatric coccidioidomycosis (also known as San Joaquin Valley Fever) cases from 2000 to 2016, with a higher incidence among those aged 12 to 17 years.[13] A review of coccidioidomycosis hospitalizations at children's hospitals in the United States from 2002 to 2007 found that most hospitalizations (96%) occurred in endemic areas, with 6% identified as having a primary or acquired immunodeficiency. During the study period, an increased incidence occurred from 2005 to 2006, especially among children with comorbid conditions. A case series of pediatric coccidioidomycosis in an infectious disease clinic in California highlighted delays in diagnosis, even in endemic regions.[14] A median delay of 57 days from symptoms onset to diagnosis was observed in children with disseminated disease, and 16 days in children with acute/pulmonary disease. Before diagnosis, most children received antibiotics for suspected bacterial infections.

Since 2000, cases of coccidioidomycosis have increased in the southwestern United States. California had observed a fivefold increase in cases.[15] Between 2000 and 2012, pediatric cases and hospitalization rates per 100,000 population increased approximately sixfold, with cases rates from 0.7 to 3.9, and hospitalizations from 0.2 to 1.2. Hispanic and African American children were at the highest risk of hospitalization. Approximately 11% of hospitalized children had an

immunocompromising condition. Only 0.2% of children had HIV. Of the 11 reported deaths, only one had an associated immunodeficiency.

Coccidioidal infection resolves once specific T cells mediate macrophage activation that inhibits or kills the fungus. In immunocompetent hosts, infections by *Coccidioides* spp. convey lifelong immunity with no reports of infection.[16] Impaired cellular immunity is the major risk factor for severe primary coccidioidomycosis and relapse of past infection. T lymphocyte-mediated immunity may be impaired by the presence of a primary or acquired immunodeficiency, such as a congenital defect, HIV infection,[17-21], or by treatment with immunosuppressive medications including corticosteroids[22,23] and tumor necrosis factor-α inhibitors.[24,25] Defects in the interferon-gamma/interleukin-12 pathway place children at risk for severe infections.[26,27] Person-to-person transmission has not been recognized; however, donor-derived coccidioidomycosis through organ donation has been documented.[28] In adults with HIV, localized pneumonia and disseminated infection[18] most often occur in individuals with CD4 T lymphocyte (CD4) cell counts <250 cells/mm^3. The threshold for increased risk in children with HIV is not well defined, but systemic fungal infections have occurred in children with significant cellular impairment when CD4 counts were ≤100 cells/mm^3 and CD4 percentages <15%.[29,30] Few cases of coccidioidomycosis have been reported in immunocompromised children. Not uncommonly, rare types of immunodeficiencies are diagnosed in children, adolescents, and adults with invasive or refractory coccidioidomycosis.[31-33] No cases of coccidioidomycosis were reported in children enrolled in the Perinatal AIDS Collaborative Transmission Study, but study sites were underrepresented in geographic regions where coccidioidomycosis is endemic.[34] Congenital coccidioidomycosis is rare, but infections have occurred following disseminated disease in mothers.[35] Infections in infants usually result from inhalation of spores in the environment.[36] In adults with HIV, antiretroviral therapy (ART) appears to be responsible for the declining incidence and severity of coccidioidomycosis; however, data are limited in children.[19,20]

Clinical Manifestations

The symptoms of coccidioidal infection can range from a mild, flu-like illness to more severe focal or disseminated disease, including pneumonia, bone and joint infection, and meningitis. Sixty percent of infected children are asymptomatic. Immunocompromised individuals and previously healthy Black, Hispanic, Native American, and Filipino people with coccidioidomycosis are at increased risk of dissemination, as are pregnant women who become infected during the second or third trimester or the immediate postpartum period.[37] The severity of disease in adults with HIV is proportional to the degree of immunosuppression. Severe forms of disease such as diffuse pulmonary infection and extrathoracic dissemination have been associated with low CD4 counts, increased HIV viral load, and a lower likelihood of having received ART. Focal pneumonitis can occur in mild to moderately immunocompromised patients. Pleural inflammation may result in effusion, empyema, and/or pneumothorax. If untreated, a coccidioidal antibody-seropositive HIV individual is at risk of serious disease, with the degree of severity inversely proportional to absolute CD4 count.[12] Bone and joint involvement are rare in people with HIV. Diffuse reticulonodular disease in an immunocompromised child with coccidioidomycosis may radiographically resemble *Pneumocystis jirovecii* pneumonia.[38] In addition, people with coccidioidomycosis may also have coinfections such as blastomycosis, toxoplasmosis, and COVID-19.[39-43] Valley Fever can mimic pulmonary and extrapulmonary tuberculosis (TB); coinfection can also occur in endemic areas.[44]

In a retrospective, observational study of 33 children with coccidioidomycosis (median age, 6 years) at a children's hospital in central California, 28 (85%) had pneumonia, 5 (15%) had osteomyelitis,

and 2 (6%) had meningitis/cerebritis.[45] Mediastinitis was common in younger children, and none of the children were immunocompromised. In another report from California, among 64 children, those with disseminated disease (n = 27) were more likely to be hospitalized. More than one-third had central nervous system (CNS) involvement. Eleven children were immunocompromised and one had HIV; however, HIV was not identified in previously healthy children.[46] A retrospective study from a tertiary care center in an endemic region of central California described 78 children with extrapulmonary manifestations of coccidioidomycosis.[47] Of those, 65% were Hispanic, 85% were without comorbid conditions, and 6% were immunocompromised. Along with pulmonary disease, bone and joints, mediastinum, CNS, cervical lymph nodes, larynx, and skin were most affected.

Children with primary pulmonary infection may present with fever, malaise, chest pain, and intermittent cough, with rare cases of hemoptysis possible. Coccidioidomycosis is commonly mistaken for bacterial pneumonia. Like with other endemic mycoses, the presence of erythema nodosum may be a key clinical finding for coccidioidomycosis in an endemic region.[48-50] Persistent fever may be a sign of extrathoracic dissemination. Musculoskeletal coccidioidomycosis has been well-described in children.[51] Common symptoms include limb swelling as well as bone and joint pain. Of children with musculoskeletal coccidioidomycosis, 29% had involvement of multiple bones, most commonly involving the craniofacial and metacarpal/metatarsal bones.[51] Children with meningitis may present with headaches, altered sensorium, vomiting, and/or focal neurologic deficits. Fever is sometimes absent, and meningismus occurs in only 50% of patients. Hydrocephalus complicating basilar inflammation, occurs in most (83% to 100%) children with coccidioidal meningitis.[52-54] Generalized lymphadenopathy, skin nodules, plaques or ulcers,[55] peritonitis,[56] and liver abnormalities may also accompany disseminated disease.

Diagnosis

Because signs and symptoms are nonspecific, the diagnosis of coccidioidomycosis should be considered in patients who reside in or have visited endemic areas.[57] The evolving changes in the geographic distribution of coccidioidomycosis may warrant a high degree of suspicion in people with compatible disease syndromes, especially those with community-acquired pneumonia living in areas with newly described cases.[5,6] Diagnostic algorithms have been developed to assist clinicians in the diagnosis of endemic mycoses, including coccidioidomycosis.[58] In patients with suspected pulmonary coccidioidomycosis, initial diagnostic testing starts with serologic assays such as enzyme immunoassays, immunodiffusion, and complement fixation. Culture, microscopy, and serology have been the standard methods used for diagnosis, but tests such as coccidioidal galactomannan antigen detection in urine can be useful for diagnosis in immunocompromised hosts.[59] Nucleic acid amplification tests (NATs) have been developed, and several are commercially available.[7] NATs and DNA probes have been used to detect *Coccidioides* spp. in tissue and soil samples.[60-62]

In patients with meningitis, cerebrospinal fluid (CSF) analysis 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 or other clinical specimens is diagnostic.[63] Stains of CSF in patients with meningitis usually are negative. Pyogranulomatous inflammation with endosporulating spherules is seen in affected tissue specimens stained with hematoxylin 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.[64] Potassium hydroxide stains are less sensitive and should not be used.[64]

Growth of *Coccidioides* spp. is supported by many conventional laboratory media used for fungal isolation and may occur within 5 days at 30°C to 37°C. Blood cultures are positive in <15% of cases.[65] CSF cultures are positive in <50% of children with meningitis.[66] In a recent study of CNS coccidioidomycosis, 4 of 30 children (13%) had a positive CSF culture, significantly lower than prior reports.[52] Cultures of respiratory specimens are often positive in adults with pulmonary disease. The laboratory should be alerted to the clinical suspicion of coccidioidal infection to minimize hazards to laboratory personnel.

Serologic assays performed by enzyme-linked immunoassay (EIA), immunodiffusion, or classical tube precipitin or complement fixation (CF) methodology that measure coccidioidal immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are valuable diagnostic aids but may be falsely negative in immunocompromised hosts.[67] 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.[68,69] IgG-specific antibodies appear later and persist for 6 to 8 months. A commercial EIA appears to be more sensitive than the older tube precipitin and CF tests and the immunodiffusion assays, although concern remains about specificity.[62] CF appears to be a more specific assay. Assays for coccidioidal antibodies in serum or body fluids such as CSF provide diagnostic and prognostic information. Cross-reactivity can occur with other endemic mycoses such as blastomycosis and histoplasmosis. Patients with coccidioidomycosis have been observed to have positive *Histoplasma* antigen results.[70] A study of 19 patients from three clinical practices in Arizona and California with acute or chronic coccidioidomycosis found 11 patients (58%) with a positive *Histoplasma* urine antigen assay.[70] In patients with acute disease, antigenuria was detected in 79% of patients. Based on these data, this assay may offer an indirect method for diagnosis. A recently developed rapid lateral flow assay is now available, but its sensitivity appears to be lower than EIA.[71] 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, detection of IgG-specific antibodies in CSF, or positive antigen.[61] Among 36 patients with coccidioidal meningitis, antigen testing of CSF demonstrated a sensitivity of 93% and specificity of 100%, while CSF cultures were positive for antigens in 7% of patients. Additionally, antibodies were identified by immunodiffusion in 67% of patients, complement fixation in 70%, and enzyme-linked immunosorbent assay–detected IgM and IgG antibodies in 8% and 85% of patients, respectively.[72]

An elevated opening pressure is often observed in patients with meningitis. Immunocompromised hosts may not have a reliable serologic response.

A *Coccidioides* EIA has been developed that detects and quantifies coccidioidal galactomannan concentrations in urine samples and is especially useful in serious infections and/or instances in which the antibody is undetectable.[59] Dissociation of immune complexes has increased the sensitivity of coccidioidal antigen detection in serum.[73] The serologic diagnosis of coccidioidomycosis might also be complicated in the presence of very high antibody levels, inducing false negative results due to a prozone phenomenon.[74,75] This occurs in assays that involve antibody–antigen binding when antibody levels are overwhelming. This effect occurs more frequently in patients with HIV and other immunodeficiencies, as well as during pregnancy.[76] Although the prozone phenomenon is most commonly associated with syphilis, it is also observed in coccidioidomycosis-endemic regions and co-occurring with various other infections. The prozone phenomenon can be overcome by testing serial serum dilutions.[77] Molecular methods of detection are commercially available at reference laboratories and may be a valuable means of confirming a diagnosis.[78] For example, meningitis has been diagnosed using real-time polymerase chain reaction (PCR) analysis of CSF.[61]

Prevention

Preventing Exposure

Patients with HIV who reside in or visit regions in which *Coccidioides* spp. are endemic cannot completely avoid infection, but the risk can be reduced by avoiding activities that may increase exposure to inhalation of spores. These activities include disturbing contaminated soil, including sports in dusty terrain, archaeological excavation, construction, and being outdoors during dust storms **(BIII).**[11,79,80] If such activities are unavoidable, use of high-efficiency respiratory filtration devices should be considered.

Preventing First Episode of Disease

No prospective studies have been published that examine the role of prophylaxis in preventing the development of active coccidioidomycosis in patients without previous (recognized) episodes of coccidioidomycosis. Some, but not all experts would provide prophylaxis with an azole (fluconazole) to coccidioidal antibody–positive patients with HIV living in regions with endemic coccidioidomycosis.[64] In a retrospective analysis of liver transplant patients residing in an endemic area, antifungal prophylaxis with fluconazole prevented coccidioidomycosis.[81] Chemoprophylaxis has been used for coccidioidal antibody–positive adults with HIV and CD4 counts <250 cells/mm^3 and who live in endemic areas.[19,30] However, given the low incidence of coccidioidomycosis in children with HIV, the potential for drug interactions, cost, and development of antifungal drug resistance, the routine use of antifungal medications for primary prophylaxis of coccidioidomycosis in children with HIV is not recommended **(BIII).**

Discontinuing Primary Prophylaxis

Not applicable.

Treatment

Treating Disease

Treatment protocols that are recommended for children with HIV with coccidioidomycosis are based on experience in studies in adults. Physicians who infrequently treat children with coccidioidomycosis should consider consulting with experts. Children with HIV who are not receiving ART at the time of diagnosis of coccidioidomycosis should receive ART along with antifungal therapy.

For years, antifungal therapy was recommended for all adults with HIV with clinically active, mild coccidioidomycosis.[82] More recently, treatment protocols used for patients without HIV have been suggested for adults with HIV[82] who are reliably receiving potent ART and who have CD4 counts >250 cells/mm^3. This applies to patients with mild infections that are not accompanied by signs suggestive of dissemination, diffuse pulmonary infiltrates, or meningitis; patients should be closely monitored to ensure ART adherence, 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. Given that comparable published experience in this setting is lacking in children, expert consultation should be sought; if treatment is elected, recommendations should be based on the assurance of continued adherence to ART, confirmation of

continued HIV suppression, maintenance of CD4 counts >250 cells/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 pneumonia), monotherapy with fluconazole or itraconazole is appropriate given their effectiveness, safety, convenient oral dosing, and pharmacodynamic parameters **(AII*).** Fluconazole (6–12 mg/kg/day, maximum dose 400 mg) and itraconazole (5–10 mg/kg/dose twice daily for the first 3 days, followed thereafter by 2–5 mg/kg/dose twice daily, maximum dosing, 200 mg every 12 hours) are preferred 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 non-meningeal coccidioidomycosis. Itraconazole (5 mg/kg body weight dose twice daily) appeared to be more effective than fluconazole for skeletal infections **(AII*).**[83] Two children with osteoarticular coccidioidomycosis who failed to respond to fluconazole monotherapy had an excellent response to itraconazole.[84] Due to increased efficacy, itraconazole is recommended for skeletal infections **(AII*).** In a 2022 study in which 83% of children received fluconazole, only 15% failed this therapy and required an alternative regimen.[51] Fluconazole is frequently used as an initial agent because it does not require therapeutic drug monitoring, it is better tolerated than itraconazole suspension, and is more likely to be covered by insurance than itraconazole suspension **(AIII).** In addition, fluconazole has fewer drug–drug interactions than itraconazole.

Severely ill patients with diffuse pneumonia and/or other signs of disseminated infection (not involving the CNS) should initially be treated with an amphotericin B preparation because these agents appear to evoke a faster therapeutic response than azoles **(AII*).**[82] Although there is no evidence that lipid preparations are more effective than amphotericin B deoxycholate, lipid formulations often are used because they are better tolerated **(AII*).** The length of amphotericin B therapy is determined by both the severity of initial symptoms and the pace of clinical improvement. Thereafter, amphotericin B is stopped, and treatment with fluconazole or itraconazole is initiated **(BIII).** Some experts initiate therapy with both amphotericin B and triazole (e.g., fluconazole) in patients with severe disseminated disease and continue the triazole after amphotericin B is stopped **(BIII).** The duration of therapy should be ≥1 year.[64,82] Lifelong maintenance therapy is recommended for immunocompromised people.

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 **(BIII).**

Itraconazole solution is preferred to the capsule formulation because it is better absorbed and can achieve serum concentrations 30% higher than those achieved with the capsules. Serum concentrations of itraconazole should be monitored and achieve a level ≥1 mcg/mL at steady state. Levels exceeding 10 mcg/mL should be followed by dose reduction **(AIII).**[85] Absorption of itraconazole solution is improved when taken with an empty stomach, while the capsule should be taken with food and acidic beverages.

A newer formulation of itraconazole called SUBA-itraconazole has been used to treat endemic mycoses. Experience in adults demonstrates similar efficacy but with less pharmacologic variability and fewer adverse events than "conventional" itraconazole.[86] Data in children are limited.[87]

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 1,200 mg/day.[82] Children usually receive 12 mg/kg/dose once daily (800 mg/day maximum) **(AII).** The 12 mg/kg dose may be required to attain serum concentrations equivalent to those in adults receiving 400 mg/day.[88,89] Some experts would begin at a dose of 15 to 23 mg/kg/day.[66] Successful therapy with posaconazole[90-92] and voriconazole[93-95] has been described in adults, but there is limited experience in children. Some experts have used intrathecal amphotericin B deoxycholate in addition to systemic azole therapy.[96] Intrathecal amphotericin B administration adds additional morbidity and is not used as part of initial therapy **(CIII).**[82] 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 era (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 an immunocompromised state, with one-third of patients in this group having HIV or AIDS.[97]

Monitoring and Adverse Events

In addition to monitoring patients for clinical improvement, some experts have recommended monitoring coccidioidal IgG antibody titers once monthly to assess response to therapy **(AIII).** If therapy is succeeding, titers should decrease progressively. A rise in titer suggests recurrence of clinical disease. However, if serologic tests initially were negative, titers during effective therapy, may initially increase briefly and thereafter decrease. 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 (including hypokalemia). Infusion-related fevers, chills, as well as 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) can also occur but are very rare in children. Intrathecal injection of amphotericin B may result in arachnoiditis.[98,99]

Triazoles can interact with other drugs metabolized by cytochrome P450-dependent hepatic enzymes, and the potential for drug interactions should be assessed before initiation of therapy **(AIII).**[85] Use of fluconazole and itraconazole appears to be safe in combination with ART. Voriconazole should be avoided in patients receiving protease inhibitors **(BIII)** or non-nucleoside reverse transcriptase inhibitors.[100] The most frequent adverse effects of fluconazole are nausea and vomiting followed by skin rash and pruritus, and some cases of Stevens-Johnson syndrome have been reported. Chronic paronychia associated with fluconazole may be associated with long-term use in children with coccidioidomycosis.[101] Resolution was observed after cessation of therapy. Asymptomatic increases in transaminases occur in 1% to 3% of patients receiving azole drugs. In patients with HIV, fluconazole at high doses can cause adrenal insufficiency. Because absorption of itraconazole varies from patient to patient, measure serum concentrations to ensure effective and nontoxic drug levels, monitor changes in dosage, and assess compliance **(BIII).**[85]

Itraconazole solution is preferred to the capsule formulation because it is better absorbed and can achieve serum concentrations 30% higher than those achieved with capsules. Serum concentrations

of itraconazole should be monitored and achieve a level ≥1 μg/mL at steady state. Levels exceeding 10 μg/mL should be followed by dose reduction **(AIII).**[85] Absorption of itraconazole solution is improved when taken on an empty stomach, whereas the capsule should be taken with food and acidic beverages.

Coccidioidomycosis-associated immune reconstitution inflammatory syndrome (IRIS) following the initiation of ART has not been reported in children and is rarely reported in adults.[102-104]

Managing Treatment Failure

The treatment of coccidioidomycosis unresponsive to standard therapy has been reviewed, with the majority of experience occurring in adults. Often patients with invasive, refractory disease may not respond to fluconazole and itraconazole treatment and may harbor resistant strains. In these situations, treatment with other azoles such as posaconazole, voriconazole, or isavuconazole may be warranted **(AII*).**[82] Posaconazole was effective in 6 adults with disease refractory to treatment with other azole, and amphotericin B and was used successfully in 11 of 15 adults (73%) whose infections were refractory to previous therapy. Posaconazole has also been effective for chronic refractory meningitis unresponsive to fluconazole.[90-92] 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.[93-95] Isavuconazole has been used as salvage therapy in coccidioidal meningitis.[105] Monotherapy with caspofungin was successful in treating disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and other adults in whom conventional therapy failed. Others have used caspofungin in combination with fluconazole and voriconazole, though some experts would not recommend echinocandins, including caspofungin. Voriconazole has been used in combination with caspofungin to treat refractory coccidioidomycosis after failing conventional therapies.[106] However, echinocandins have limited activity against *Coccidioides* spp. The use of these agents is not recommended by fungal experts as frontline therapy. Azoles remain the preferred agents for salvage therapy **(AII*).**[107]

Adjunctive interferon-gamma (IFN-γ) has been successful in treating people with refractory coccidioidomycosis who failed other therapies.[108,109] A work-up for underlying immunodeficiencies is generally recommended in children who were previously healthy and who develop invasive, severe coccidioidomycosis disease. Recent studies have investigated the use of monoclonal antibodies in children with disseminated coccidioidomycosis with impaired cytokine receptor signaling, with protocols developed for the use of dupilumab—a monoclonal antibody that blocks the alpha chain common to the interleukin-4 and interleukin-13 receptors—and interferon-gamma treatment as adjunctive therapy to antifungals.[33] Interferon-γ in combination with dupilumab has been successful in treating disseminated coccidioidomycosis in a previously healthy child.[33] However, no controlled clinical studies or data exist for children; thus IFN-γ is not recommended for use in children with HIV **(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 deoxycholate into the intrathecal, ventricular, or intracisternal spaces, with or without concomitant azole treatment, have been used successfully **(AIII).** Liposomal amphotericin B has been used to treat relapsed coccidioidal meningitis.[110] A consensus panel of experts recommended a trial of liposomal amphotericin B based on case reports with documented efficacy, but amphotericin B deoxycholate was not recommended **(AIII).**[111] When patients receiving liposomal amphotericin B are being transitioned to an azole agent, many experts discontinue the amphotericin B formulation only once

azole serum levels have reached steady state and are therapeutic. The basilar inflammation that characteristically accompanies coccidioidal meningitis often results in obstructive hydrocephalus requiring the 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.[112] 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 disease 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 CD4 counts <250/mm^3 or CD4 percentages <15% **(BIII).**[82]

Discontinuing Secondary Prophylaxis

In disseminated infection, continuing 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, because of the high risk of relapse **(AII*).** In adults with HIV and focal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 counts >250/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. The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children has not been studied. Therefore, in children with HIV, 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).**

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) per dose IV or PO once daily, *or* • For Coccidioidal Meningitis: o Continue initial treatment with fluconazole (12 mg/kg body weight per dose IV or PO once daily)	Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily	Secondary Prophylaxis Indicated • Prior meningitis or disseminated disease • Milder disease if CD4 count <250 cells/mm^3 or CD4 percentage <15%. Criteria for Discontinuing Secondary Prophylaxis • Lifelong therapy for meningitis or disseminated disease • Consider lifelong therapy for milder disease, regardless of ART or immune reconstitution
Treatment	Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease • Liposomal amphotericin B preparation at a dose of 5 mg/kg body weight IV once daily (dose can be increased to as much as 10 mg/kg body weight IV once daily for life-threatening infections) • Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily, until clinical improvement • Liposomal amphotericin B is the treatment of choice with similar efficacy with fewer adverse events. • After the patient is stabilized, therapy with an azole (fluconazole or itraconazole) can be substituted and continued to complete a 1-year	Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease *If unable to use amphotericin B:* • Fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or by mouth once daily. • Treatment is continued for a total of 1 year, followed by secondary prophylaxis.	Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful. Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent. Some experts initiate an azole during amphotericin B therapy. Others defer initiation of the azole until after amphotericin B is stopped. For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children. Options should be discussed with an expert in the treatment of coccidioidomycosis. Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease.

Dosing Recommendations for Prevention and Treatment of Coccidioidomycosis

Indication	First Choice	Alternative	Comments/Special Issues
	course of antifungal therapy.		Therapy with amphotericin B results in a more rapid clinical response in severe, non-meningeal disease.
	Mild-to-Moderate Non-Meningeal Coccidioidal Infection • Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily for 6–12 months and clinical improvement	Mild-to-Moderate Non-Meningeal Coccidioidal Infection • Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) per dose IV or PO three times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily thereafter for 6–12 months and clinical improvement • *Age ≥13 Years:* Posaconazole oral (delayed-release tablets), 300 mg twice daily for two doses, followed by 300 mg daily for 6–12 months and clinical improvement	Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful. Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent. For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children. Options should be discussed with an expert in the treatment of coccidioidomycosis. Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm^3 or CD4 percentage <15%.
	Coccidioidal Meningitis • Lifelong fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or PO once daily	Coccidioidal Meningitis • IV liposomal amphotericin B plus intrathecal amphotericin B deoxycholate followed by secondary prophylaxis	For treatment failure, can consider posaconazole, isavuconazole, or voriconazole. Chronic suppressive therapy (secondary prophylaxis) with fluconazole is continued lifelong for meningeal disease. Options for treatment and secondary prophylaxis should be discussed with an expert in the treatment of coccidioidomycosis in children.

Key: CD4 = CD4 T lymphocyte; IV = intravenous; PO = oral

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COVID-19

Updated: July 03, 2024
Reviewed: July 03, 2024

Panel's Recommendations
COVID-19 Vaccination and Pre-Exposure Prophylaxis to Prevent COVID-19, Including Severe Disease • Children with HIV aged ≥6 months should receive COVID-19 vaccination, regardless of CD4 T lymphocyte cell count or viral load (AI). • Household members and close contacts of children with HIV aged ≥6 months should receive COVID-19 vaccination (AIII). • Although vaccine responses are likely to improve after initiation of antiretroviral therapy, vaccination against COVID-19 should not be delayed while awaiting immune reconstitution (AIII). • Pemivibart (Pemgarda) should be considered for the prevention of COVID-19 in children aged ≥12 years and who weigh ≥40 kg with HIV with severe immunosuppression (stage 3 – see HIV Infection Stage table in the Introduction) regardless of COVID-19 vaccination status (BIII) and may be considered for the prevention of COVID-19 in children aged ≥12 years and who weigh ≥40 kg with HIV with moderate to no immunosuppression (stage 1 or 2 – see HIV Infection Stage table in the Introduction) in whom COVID-19 vaccines are contraindicated or unavailable (CIII). Monoclonal antibodies, including pemivibart, are not a substitute for vaccination in people who are eligible for COVID-19 vaccines. Treatment of COVID-19 in the Outpatient Setting • Ritonavir-boosted nirmatrelvir (Paxlovid) should be considered in the outpatient setting for treatment of laboratory-confirmed or clinically suspected mild to moderate COVID-19 in children with HIV who are aged ≥12 years, weigh ≥40 kg, and are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by the Centers for Disease Control and Prevention (CDC) (BI*). • Ritonavir-boosted nirmatrelvir should be started within 5 days of symptom onset (BI*). • Ritonavir-boosted nirmatrelvir may be administered with antiretrovirals, including those that contain ritonavir or cobicistat, without any interruption of or modification to the antiretroviral therapy (AIII). • Remdesivir (Veklury) may be considered in the outpatient setting for treatment of laboratory-confirmed or clinically suspected mild to moderate COVID-19 in children with HIV who are aged ≥28 days, weigh ≥3 kg, and are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC (CIII). • Remdesivir should be started within 7 days of symptom onset, but its use could be considered in children with HIV with severe immunosuppression who have had >7 days of symptoms (CIII). • For non-hospitalized children with HIV aged ≥12 years at high risk of progressing to severe COVID-19, ritonavir-boosted nirmatrelvir is the preferred treatment, but remdesivir may be considered if ritonavir-boosted nirmatrelvir is unavailable or contraindicated (BI*). Treatment of COVID-19 in the Inpatient Setting • Remdesivir should be considered for treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who are aged ≥28 days, weigh ≥3 kg, require hospitalization, and are receiving supplemental oxygen (BI*). • Remdesivir should be administered for treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who are aged ≥28 days, weigh ≥3 kg, are severely or critically ill, have a rapidly increasing oxygen requirement, and/or are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC (AI*).

- Remdesivir should be started within 7 days of symptom onset, but its use could be considered in children with HIV with severe immunosuppression who have had >7 days of symptoms (CIII).
- Corticosteroids (such as dexamethasone) should be considered for the treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who require hospitalization and are receiving supplemental oxygen (BIII).
- Corticosteroids should be administered for the treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who are severely or critically ill, have a rapidly increasing oxygen requirement, and/or who are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC (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 postpubertal adolescents

Epidemiology

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus (type) 2 (SARS-CoV-2) virus, which was initially identified in December 2019 and quickly spread around the globe, causing a pandemic. The virus is spread through respiratory droplets and small particles that are inhaled during close person-to-person contact or transmitted through touching mucous membranes with hands that have been contaminated by the virus.[1] The mean incubation period for SARS-CoV-2 is 3 to 5 days, with more recent variants associated with shorter incubation periods and nearly all infections occurring within 14 days of exposure.[2] Viral shedding begins prior to the onset of symptoms, peaks around the time of symptom onset, and gradually declines over the next 7 to 10 days. Transmission of infectious virus is unlikely after 10 days of illness; however, prolonged shedding for 20 days or longer has been described in persons with immunosuppression, including those with advanced or untreated HIV infection.[3-6]

SARS-CoV-2 has evolved over time through mutations in its viral genome. Variants of interest or variants of concern are assigned letters of the Greek alphabet by the World Health Organization (WHO).[7] Some new variants and some sublineages may have increased transmissibility or virulence, ability to evade the humoral immunity induced by vaccination or previous infection, or features that impact the effectiveness of diagnostics and therapeutics. Within the United States, the proportions of variants circulating in different parts of the country are reported on the Centers for Disease Control and Prevention (CDC) Data Tracker website.[8]

As of September 9, 2023, nearly 200,000 children under 18 years have required hospital admission for COVID-19, and more than 1,600 children have died.[8,9] COVID-19 has affected people in different racial and ethnic groups unequally. People within racial and ethnic minority groups are at increased risk of SARS-CoV-2 acquisition, COVID-19–related hospitalization, and death.[10-15] Importantly, these communities have also been disproportionately affected by the HIV epidemic.

Clinical Manifestations

SARS-CoV-2 infection can cause a range of clinical presentations, from asymptomatic infection to mild respiratory symptoms to severe organ dysfunction and death. Cough, congestion, fever, myalgias, and headache are the most common presenting symptoms of COVID-19 in adults and children. Pediatric patients with COVID-19 may present with symptoms of croup or bronchiolitis. Gastrointestinal manifestations of COVID-19 occur infrequently but are reported more often in younger populations.[15-17] Disorders of smell and taste (i.e., anosmia and dysgeusia) were reported with early variants of SARS-CoV-2, but are less common with more recent variants.[18] A range of dermatologic findings, including various rashes (maculopapular, urticarial, petechial, and/or vesicular) and chilblains-like lesions on the digits, have also been reported with COVID-19.[19]

Children appear less likely to become severely ill with COVID-19 than adults.[8] Severe COVID-19 in children can lead to pneumonia, acute respiratory distress syndrome, shock, and multiple organ dysfunction. Well-described complications include cardiac (e.g., arrhythmia, myocardial injury, heart failure), neurologic (e.g., seizures, encephalopathy), thromboembolic, hyperinflammatory syndromes, and death. Underlying conditions that are associated with higher rates of severe COVID-19 in children include asthma, obstructive sleep apnea, chronic lung disease, cardiac disease, neurologic disorders, obesity, diabetes, prematurity (in young infants), immunocompromising conditions (other than HIV), and medical complexity/dependence on medical technology (such as tube feeding or chronic respiratory support).[15,16,20-23] Severe COVID-19 (i.e., resulting in hospitalization, intensive care unit [ICU] admission, or mechanical ventilation) has been reported less commonly in children with later variants of SARS-CoV-2 compared to earlier variants.[17,21,24,25]

It is unclear whether people with HIV are at increased risk of severe COVID-19. Observational cohort studies have shown conflicting results, with some reporting higher rates of hospitalization, ICU admission, mechanical ventilation support, and/or mortality among adults with HIV and others showing no increased risk associated with HIV infection.[26-42] Several studies identified an increased risk of severe COVID-19 among adults with advanced or untreated HIV infection compared to those on antiretroviral treatment (ART) with no evidence of immunosuppression.[34-38,41-43] Few publications have described the outcomes of children or adolescents with HIV who acquire SARS-CoV-2, but those available report mild COVID-19 symptoms and/or no increased risk of severe COVID-19 among children or adolescents with HIV.[44-48]

Following infection with SARS-CoV-2, which may be asymptomatic, some children may experience a post-acute manifestation of the infection, such as multisystem inflammatory syndrome in children (MIS-C) or post-acute sequelae of SARS-CoV-2 (PASC; also known as “long COVID” or “long-hauler syndrome”). An increased rate of some autoimmune complications, such as new-onset type 1 diabetes, has also been identified in the post–COVID-19 period.[49,50]

PASC is a heterogenous disorder that has been described in 4% to 66% of children after acute COVID-19.[51] The presentation of PASC may include any of a wide-ranging constellation of symptoms that involve multiple body systems, such as:

- Neurologic (fatigue, sleep disorders, attention disorders, “brain fog,” headaches)
- Psychiatric (anxiety, depression, post-traumatic stress disorder)
- Pulmonary (cough, dyspnea)

- Cardiac (chest pain, palpitations, dizziness, exercise intolerance, autonomic dysfunction, syncope)
- Otolaryngologic (anosmia, dysgeusia)
- Musculoskeletal (arthralgias, myalgias)
- Gastrointestinal (nausea, vomiting, diarrhea, abdominal pain)

A multidisciplinary group defined PASC in children as involving one or more persistent physical symptoms, which may fluctuate and relapse, that lasts for at least 12 weeks after confirmed initial SARS-CoV-2 infection, impairs daily function, and cannot be explained by an alternative diagnosis after initial testing.[52] Limited data suggest that adults with HIV may be at higher risk of PASC than adults without HIV, but more research is needed on the incidence of PASC in children with HIV.[53-55]

MIS-C is a relatively rare postinfectious hyperinflammatory condition occurring in <1% of children 2 to 6 weeks after acute COVID-19, including following mild or asymptomatic infection.[56,57] MIS-C has been reported less commonly in children with later variants of SARS-CoV-2 compared to earlier variants. Symptoms may overlap with those of Kawasaki syndrome or toxic shock syndrome; however, MIS-C typically occurs in older children and adolescents (median age 8-9 years), whereas Kawasaki syndrome classically occurs in younger children <5 years of age.[58-61] CDC developed new case definitions for confirmed and probable MIS-C in January 2023, which include age <21 years, fever, clinical severity requiring hospitalization or resulting in death, C-reactive protein ≥3 mg/dL, new-onset manifestations in at least two categories (cardiac, mucocutaneous, shock, gastrointestinal, hematologic), absence of a more likely alternative diagnosis, and laboratory-confirmed SARS-CoV-2 infection (confirmed case) or exposure (probable case) in the last 60 days.[62] More research is needed to understand MIS-C outcomes among children with HIV.

Diagnosis

The approach to diagnosing acute SARS-CoV-2 infection is identical in children with and without HIV, involving antigen tests using upper respiratory tract samples or nucleic acid amplification tests (NAAT), which are considered the most accurate. Many rapid antigen tests are available for home use. Some of the NAAT and antigen diagnostic tests for SARS-CoV-2 are approved for use by the U.S. Food and Drug Administration (FDA), while others are available under an Emergency Use Authorization (EUA).[63]

SARS-CoV-2 serologic (i.e., antibody) tests can be used to determine whether prior exposure to SARS-CoV-2 has occurred through either vaccination or infection; however, serologic tests should not be used to make a diagnosis of acute COVID-19 because it can take 21 days or longer after symptom onset for seroconversion to occur.[64,65] SARS-CoV-2 serologic tests may have variable sensitivity and specificity, may detect different isotypes of immunoglobulins (i.e., immunoglobulin G, immunoglobulin A, and/or immunoglobulin M), and may be subject to cross-reactivity to antibodies from other coronaviruses. For these reasons, SARS-CoV-2 serologic tests **should not** be used to guide decisions about the use of vaccines, monoclonal antibodies, or other therapeutics to prevent or treat acute COVID-19 **(AIII).**

Prevention Recommendations

Preventing Exposure

Several personal preventative measures can be implemented to decrease the likelihood of SARS-CoV-2 spreading in community settings. Personal hygiene measures include frequent handwashing or use of an alcohol-based hand sanitizer and covering the nose and mouth while coughing and sneezing. During periods of high community transmission, the risk of SARS-CoV-2 acquisition can be decreased by avoiding crowds and close contact with people outside of the household and ensuring adequate ventilation of indoor spaces. Proper use of a well-fitted mask or face covering can also help decrease community spread of SARS-CoV-2, primarily by containing the secretions of infected persons, but also by reducing exposure of the mask wearer to the virus, with the degree of protection offered to the mask wearer dependent upon the filtration efficacy of the mask (with N95 masks having the highest filtration efficacy, followed by disposable medical masks, and finally by cloth masks).[66-68] Mask wearing is most beneficial during periods of high community transmission in settings where social distancing is difficult or impossible, as well as indoor settings with poor ventilation. People who acquire SARS-CoV-2 should isolate at home until at least 24 hours after their symptoms begin improving and fever has resolved to prevent spreading the infection to others.[69,70]

In the health care setting, infection prevention interventions to reduce the spread of SARS-CoV-2 include identification and isolation of people with infection, use of personal protective equipment, proper hand hygiene, and environmental disinfection. When caring for patients with COVID-19, health care providers should use a particulate respirator (i.e., N95 mask) during all aerosol-generating procedures and potentially during all interactions with the patient.[71] During periods of high SARS-CoV-2 community transmission, institutions may decide to implement the universal use of face masks for everyone in a health care setting (e.g., employees, visitors).

Preventing Disease

COVID-19 vaccination effectively prevents severe outcomes such as hospitalization and post-acute COVID-19 syndromes (e.g., MIS-C and PASC) in children.[72-86] While there is evidence that vaccine effectiveness wanes over time, protection against severe disease (ICU admission, mechanical ventilation, or death) is more durable.[87,88] Several successive formulations of COVID-19 vaccines have been developed and approved or authorized for use by the FDA in an effort to best target circulating variants. For more information on currently recommended vaccine products and schedules, see CDC's Use of COVID-19 Vaccines in the United States. In the United States, COVID-19 vaccines have been authorized for children aged ≥6 months since June 2022.[89] Clinical trials evaluating COVID-19 vaccines in infants <6 months of age are ongoing (e.g., NCT05584202). Although no COVID-19 vaccines are yet approved for children <6 months of age, maternal immunization during pregnancy has been shown to increase antibody transfer and provide protection to infants for the first 6 months of life.[90,91]

All children with HIV aged ≥6 months should receive age-appropriate COVID-19 vaccines, including updated vaccines as part of routine prevention, regardless of CD4 T lymphocyte (CD4) cell count or viral load **(AI).** Household members and close contacts of children with HIV aged ≥6 months should also receive COVID-19 vaccines to prevent exposure to the child **(AIII).** Refer to CDC's Use of COVID-19 Vaccines in the United States for the most up-to-date information about

the COVID-19 vaccines available to children by age, immunocompromised status, and the recommended dosing intervals.[89] Thus far, studies of adults and children with HIV show that COVID-19 vaccines are safe and immunogenic, but humoral responses are lower in people with advanced or untreated HIV.[48,92-102] Although vaccine responses are likely to improve after initiation of ART, vaccination against COVID-19 should not be delayed while awaiting immune reconstitution **(AIII).** Children with HIV may receive additional doses of COVID-19 vaccines, as indicated by CDC's COVID-19 vaccination guidance for people who are moderately or severely immunocompromised, if they have stage 3 HIV infection (see HIV Infection Stage table in the Introduction), history of an AIDS-defining illness without immune reconstitution, clinical manifestations of symptomatic HIV, or untreated HIV infection.

There are very few contraindications or precautions associated with the COVID-19 vaccines, and these precautions are identical for children with and without HIV.[89] Common side effects that may occur after receipt of vaccines include local reactions (pain, swelling, or redness at the injection site), ipsilateral axillary lymphadenopathy, and such systemic reactions as fever, fatigue, headache, or myalgias. Anaphylaxis or syncope may occur rarely in the immediate post-vaccination period. Myocarditis and/or pericarditis has been described (see CDC's Clinical Considerations: Myocarditis and Pericarditis after Receipt of COVID-19 Vaccines) most frequently among adolescent or young adult males, typically in the week after receiving a second dose or subsequent dose of a messenger RNA (mRNA) COVID-19 vaccine. Myocarditis or pericarditis is estimated to be a rare outcome (up to two cases per 10,000 mRNA vaccine doses), and nearly all cases are mild and result in full recovery.[103] In addition, cardiac complications are estimated to occur at a rate two- to sixfold higher among adolescent males ages 12 to 17 years after SARS-CoV-2 infection than after mRNA vaccination.[104]

Pemivibart (Pemgarda™) is a recombinant human monoclonal antibody that was authorized by the FDA in March 2024 for use as pre-exposure prophylaxis against COVID-19 in adults and adolescents aged ≥12 years and who weigh ≥40 kg with moderate-to-severe immunocompromise (including those with advanced or untreated HIV infection) who are unlikely to have an adequate response to COVID-19 vaccination.[105,106] Pemivibart is administered intravenously in a health care setting with a post-infusion observation period of 2 hours due to the possibility of anaphylaxis. Doses can be repeated every 3 months if the risk of exposure to SARS-CoV-2 and moderate-to-severe immunocompromise persist. While pemivibart is the only available option for pre-exposure prophylaxis, it may be logistically challenging to administer and may not be available in all locations. For children aged ≥12 years and who weigh ≥40 kg with HIV, the Panel on Opportunistic Infections in Children with and Exposed to HIV (the Panel) recommends that pemivibart be considered for the prevention of COVID-19 in those with severe immunosuppression (stage 3 – see HIV Infection Stage table in the Introduction) regardless of COVID-19 vaccination status **(BIII)** and that it may be considered for those with moderate to no immunosuppression (stage 1 or 2 – see HIV Infection Stage table in the Introduction) in whom COVID-19 vaccines are contraindicated or unavailable **(CIII).** Monoclonal antibodies, including pemivibart, are not a substitute for vaccination in people who are eligible for COVID-19 vaccines. In individuals recently vaccinated against COVID-19, pemivibart should be administered at least 2 weeks after the most recent vaccination. Pemivibart is not authorized for post-exposure prophylaxis against COVID-19.

Treatment Recommendations

Treating Disease

The majority of pediatric SARS-CoV-2 infections are asymptomatic or mildly symptomatic, including in children and youth with HIV.[48] Isolation and supportive care with antipyretics, analgesics, hydration, and rest are the mainstays of treatment. Children who present with syndromes consistent with croup, bronchiolitis, or an asthma exacerbation and test positive for SARS-CoV-2 should receive supportive care and adjunctive treatments (including corticosteroids, if indicated) as per standard of care.

In general, the management of COVID-19 in people with HIV is similar to the management of people without HIV, with two exceptions: (1) people with advanced or untreated HIV who have COVID-19 and for whom there is concern for clinical worsening should be evaluated for opportunistic infections, and (2) people with HIV may be eligible for certain antiviral medications due to having a higher risk of progression to severe COVID-19. Of note, no clinical trials have been performed to specifically evaluate the efficacy of any currently available antiviral medications that target SARS-CoV-2 among people with HIV. In addition, very few published studies have evaluated these medications in children. Recommendations for the therapeutic management of children with COVID-19 are largely extrapolated from adult safety and efficacy data, established management of other viral infections in children, and expert opinion. The decision to use antiviral medications in children with COVID-19 should take into account the child's risk factors for progression to severe disease, including medical comorbidities, degree of immunosuppression, and history of vaccination against COVID-19.

As the SARS-CoV-2 virus evolves over time, the efficacy of antiviral medications used to treat COVID-19 may change. Antiviral drugs currently available for use in pediatric patients <18 years of age that have activity against currently circulating SARS-CoV-2 variants include remdesivir (available to those aged ≥28 days) and ritonavir-boosted nirmatrelvir (Paxlovid) (available to those aged ≥12 years). Molnupiravir is an antiviral with an EUA for people ≥18 years of age; therefore, it will not be discussed further in this guidance.

Remdesivir (Veklury)

Remdesivir (Veklury) is approved by the FDA for the treatment of COVID-19 in adults and children aged ≥28 days and who weigh ≥3 kg who are hospitalized with COVID-19 and for those with mild to moderate COVID-19 who are not hospitalized and are at high risk of progression to severe disease. In clinical trials of non-hospitalized adolescents and adults at high risk of progression to severe COVID-19, remdesivir was associated with significant reductions in hospitalization or death.[107,108] Clinical trials that evaluated remdesivir in hospitalized adults with severe COVID-19 consistently showed benefit among a subgroup of patients who required supplemental oxygen but not mechanical ventilation.[109-112] Publications describing the use of remdesivir in children are limited to one single-arm, open-label study of 53 hospitalized children and a small number of case series; these studies reported high rates of clinical recovery and few adverse events.[113-116]

Based on these data, the Panel recommends that remdesivir may be considered in the outpatient setting for treatment of laboratory-confirmed or clinically suspected mild to moderate COVID-19 in children with HIV who are aged ≥28 days and weigh ≥3 kg and are at high risk of progressing to

severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC **(CIII).** For non-hospitalized children with HIV aged ≥12 years and at high risk of progressing to severe COVID-19, ritonavir-boosted nirmatrelvir is the preferred treatment, but remdesivir may be considered if ritonavir-boosted nirmatrelvir is unavailable or contraindicated **(BI*).** For non-hospitalized children with HIV aged <12 years and at high risk of progressing to severe COVID-19, remdesivir is currently the only treatment option but may be logistically challenging to administer and may not be available in all locations.

Among hospitalized children with HIV who are aged ≥28 days and weigh ≥3 kg with laboratory-confirmed or clinically suspected acute COVID-19, remdesivir should be considered in children who are receiving supplemental oxygen **(BI*)** and should be administered in children who are severely or critically ill, have a rapidly increasing oxygen requirement, and/or who are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC **(AI*).**

Remdesivir is administered intravenously once daily for 3 days to non-hospitalized patients and for 5 days or until discharge (whichever occurs first) in hospitalized patients. The duration of remdesivir for hospitalized patients who are critically ill or have immunosuppression can be extended to 10 days. Ideally, remdesivir should be started within 7 days of symptom onset, as active viral replication has often ceased after this time in the majority of previously healthy patients. However, in children with HIV with severe immunosuppression who may have prolonged viral replication and shedding, antiviral therapy could be considered even if presenting with >7 days of symptoms **(CIII).** Common side effects attributed to remdesivir include nausea/vomiting and elevation of serum transaminases. Although remdesivir has potential for drug–drug interactions, the potential for interactions with antiretroviral (ARV) drugs is thought to be unlikely. Providers should consult a drug interactions resource, such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance.[117]

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Ritonavir-boosted nirmatrelvir (Paxlovid) is an oral protease inhibitor (PI) that has an EUA for the treatment of COVID-19 in children aged ≥12 years and who weigh ≥40 kg who are at high risk of progression to severe disease. In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 89% compared to placebo in non-hospitalized adults (≥18 years) with COVID-19 who were at high risk of progression to severe disease.[118] It is unclear whether any participants had HIV. Clinical trials, such as EPIC-Peds (NCT05261139),[119] are underway to evaluate the safety and efficacy of ritonavir-boosted nirmatrelvir in children. A case series of nine children who received ritonavir-boosted nirmatrelvir reported few adverse events and no hospitalizations after receiving treatment.[120] Ritonavir-boosted nirmatrelvir is expected to achieve similar drug exposure in adolescents aged ≥12 years and who weigh ≥40 kg as in adults, and there is extensive experience with the use of ritonavir in children.[121] Based on these data, the Panel recommends that ritonavir-boosted nirmatrelvir should be considered in the outpatient setting for the treatment of laboratory-confirmed or clinically suspected mild to moderate COVID-19 in children with HIV who are aged ≥12 years and weigh ≥40 kg who are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC **(BI*).**

Ritonavir-boosted nirmatrelvir may be administered with other ARVs, including those that contain ritonavir or cobicistat, without any interruption or modification to the child's usual antiretroviral therapy **(AIII).**[122] Children taking an ARV regimen that includes ritonavir or cobicistat should be monitored for increased side effects (e.g., nausea, vomiting, diarrhea, abdominal pain, jaundice, hepatic transaminase elevations) while taking ritonavir-boosted nirmatrelvir, but the doses of ritonavir-boosted nirmatrelvir and/or the other ARVs do not need to be adjusted. Patients with untreated or poorly controlled HIV could theoretically develop PI resistance while taking ritonavir-boosted nirmatrelvir. Ritonavir-boosted nirmatrelvir has potential for drug–drug interactions due to being both a cytochrome P450 (CYP) 3A inhibitor and a CYP3A substrate. Providers should consult the FDA Paxlovid Emergency Use Authorization Fact Sheet for Healthcare Providers, the Infectious Diseases Society of America Management of Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid): Resource for Clinicians, and/or the University of Liverpool COVID-19 Drug–Drug Interaction website for guidance on drug–drug interactions. Renal and hepatic function should be evaluated prior to initiating ritonavir-boosted nirmatrelvir, and doses should be adjusted if needed.[121] Ritonavir-boosted nirmatrelvir should be started within 5 days of symptom onset **(BI*)** and administered orally twice daily for 5 days. Patients should be advised that a small proportion of people experience "rebound" (i.e., return of symptoms, testing positive after a previous negative test, or both) 2 to 8 days after taking ritonavir-boosted nirmatrelvir.[123] The potential for viral rebound should not dissuade providers from offering ritonavir-boosted nirmatrelvir to patients who are at high risk of progressing to severe COVID-19 and could potentially benefit from its use **(AIII).** Other potential side effects of ritonavir-boosted nirmatrelvir include gastrointestinal upset (nausea, vomiting, diarrhea), altered taste, and increased blood pressure.

Other Treatment Considerations

Corticosteroids have demonstrated benefit in hospitalized adults with severe COVID-19. The RECOVERY trial reported a decrease in 28-day all-cause mortality among hospitalized adults ≥18 years of age who received 10 days of dexamethasone, with the greatest effect among adults receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO), a moderate effect among patients receiving supplemental oxygen or noninvasive positive pressure ventilation, and no effect among patients who did not require supplemental oxygen.[124] A small number of participants (<1%) had HIV. No clinical trials have evaluated the efficacy of corticosteroids in children with COVID-19. However, given the strong safety record of corticosteroids and abundant pediatric experience with corticosteroids in other settings, the possible benefits likely outweigh the potential risks in critically ill and severely ill children. Therefore, the Panel recommends that corticosteroids (such as dexamethasone) should be considered for treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who require hospitalization and are receiving supplemental oxygen **(BIII)** and should be administered for treatment of laboratory-confirmed or clinically suspected acute COVID-19 in children with HIV who are severely or critically ill, have a rapidly increasing oxygen requirement, and/or who are at high risk of progressing to severe COVID-19 due to advanced or untreated HIV or another high-risk condition as defined by CDC **(AIII).**

Dexamethasone can be administered to hospitalized children with COVID-19 orally or intravenously for ≤10 days. Dexamethasone has potential for drug–drug interactions; of particular importance to children with HIV is a potential interaction with non-nucleoside reverse transcriptase inhibitors (NNRTIs), which may result in decreased serum concentrations of either dexamethasone or the NNRTI, depending on which NNRTI is used. Providers should consult a drug interactions resource,

such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance. Alternative corticosteroids, such as hydrocortisone or methylprednisolone, may be considered if dexamethasone is not available or if alternative corticosteroids are being administered for another indication. Except for considering potential drug–drug interactions, recommendations for the use of corticosteroids in children hospitalized with severe COVID-19 are no different for children with and without HIV. Corticosteroids should be avoided in non-hospitalized children with COVID-19 unless they are used for an indication (e.g., croup, asthma exacerbation).

Anti-inflammatory medications—such as anakinra, baricitinib, tocilizumab, and tofacitinib—have been used in hospitalized adults with severe COVID-19. Of note, the EUAs of baricitinib and tocilizumab for hospitalized patients with COVID-19 include children as young as 2 years of age.[125,126] Several of these medications have been used in other pediatric rheumatologic or inflammatory disorders. However, there is less experience with the use of these anti-inflammatory agents than with corticosteroids in children with COVID-19. These anti-inflammatory medications can be considered on a case-by-case basis in children with HIV who are hospitalized with severe COVID-19 (i.e., requiring mechanical ventilation or ECMO, with critical illness, or with evidence of hyperinflammation) who are not improving despite treatment with antivirals and corticosteroids **(CIII).** The choice of anti-inflammatory agent may differ among institutions; consultation with a pediatric rheumatologist is suggested. Recommendations for the use of anti-inflammatory medications in children hospitalized with severe COVID-19 are no different for children with and without HIV.

Anticoagulation is often used in hospitalized adults with COVID-19 to prevent thromboembolic disease. In two large case series of children hospitalized with acute symptomatic COVID-19, between 1% to 2% experienced a thromboembolic complication.[127,128] No trials to define the optimal approach to anticoagulation have been conducted among hospitalized children with COVID-19. Prophylactic anticoagulation can be considered in hospitalized children with HIV with COVID-19 according to local institutional guidelines and consideration of the patient's underlying risk factors for thromboembolic disorders **(CIII).** Recommendations for the use of prophylactic anticoagulation in children hospitalized with COVID-19 are no different for children with and without HIV.

Managing Treatment Failure

In children hospitalized for severe COVID-19, high-quality supportive care in a pediatric critical care unit is vital to recovery. The duration of remdesivir can be extended to 10 days in critically ill patients that have not shown substantial improvement by Day 5. Corticosteroids can also be used for up to 10 days in children who are severely or critically ill. Immune modulation (e.g., treatment with anti-inflammatory medications, such as anakinra, baricitinib, tocilizumab, and tofacitinib) has been used in children who are not improving despite treatment with antivirals and corticosteroids.

Managing Multisystem Inflammatory Syndrome in Children

The approach to treating MIS-C is identical in children with and without HIV. Supportive management is tailored to the patient's presenting symptoms and degree of clinical severity and should include fluid resuscitation, inotropic support, and respiratory support as needed. MIS-C is typically treated with anti-inflammatory medications, although the choice of agents (e.g., corticosteroids, intravenous immune globulin, anakinra, infliximab), dose, and duration used

varies between institutions. The American College of Rheumatology has developed clinical guidance documents for the management of MIS-C.

Managing Post-acute Sequelae of SARS-CoV-2

The approach to treating PASC is identical in children with and without HIV. Some symptoms (e.g., anosmia) may require only watchful waiting, whereas others (e.g., heart palpitations, psychiatric symptoms) may require diagnostic testing and/or referral to a subspecialist. Symptoms of fatigue and exercise intolerance may benefit from a gradual increase in physical activity through an exercise program, possibly with oversight from a physical or occupational therapist. In some locations, multidisciplinary clinics have been formed to manage pediatric PASC, but these are not likely to be accessible for all children. Further guidance on the management of pediatric PASC can be found in published consensus statements from the Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 Infection Collaborative and the American Academy of Pediatrics.

Management of HIV During the COVID-19 Pandemic

During periods of elevated community transmission of SARS-CoV-2, clinicians managing HIV should make every effort to maintain routine health care visits and viral load monitoring. Health care facilities should offer virtual (telehealth) visits, if possible, for patients isolating at home or patients who wish to avoid potential exposure to COVID-19. The importance of maintaining adherence to ART should be emphasized, and clinicians should ensure that people with HIV can access an adequate supply of ART. One such strategy includes providing refills every 3 or 6 months instead of every 30 days. There is no evidence that any ARVs used for the treatment of HIV (e.g., lopinavir/ritonavir, boosted darunavir, or tenofovir disoproxil fumarate/emtricitabine) have efficacy against SARS-CoV-2; therefore, children with HIV should not change their ARV regimen in an effort to prevent or treat COVID-19 **(AIII).** When children with HIV acquire SARS-CoV-2, regardless of whether they require hospitalization or treatment for COVID-19, they should continue their usual ART **(AIII).** Clinicians should note that lymphopenia is a common laboratory finding in patients with COVID-19 (and MIS-C); therefore, in patients with HIV, the CD4 counts obtained during acute COVID-19 or MIS-C may not accurately reflect the HIV disease stage.

Dosing Recommendations for Prevention and Treatment of COVID-19

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	COVID-19 vaccines and updated vaccines	Pemivibart (Pemgarda) *Aged ≥12 Years and ≥40 kg* • Pemivibart injection solution: 4,500 mg administered as a single IV infusion	COVID-19 Vaccination Indicated for— • All children with HIV aged ≥6 months regardless of CD4 cell count or viral load • Household members and close contacts of children with HIV aged ≥6 months For up-to-date vaccine guidance, see CDC's Use of COVID-19 Vaccines in the United States webpage. Children with HIV may qualify for additional doses of COVID-19 vaccines if they have stage 3 HIV infection (see HIV Infection Stage table in the Introduction), history of an AIDS-defining illness without immune reconstitution, clinical manifestations of symptomatic HIV, or untreated HIV infection. Pemivibart Indicated for— • Adults and adolescents aged ≥12 years and who weigh ≥40 kg with moderate-to-severe immunocompromise (including those with advanced or untreated HIV infection) who are unlikely to have an adequate response to COVID-19 vaccination.
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	Non-hospitalized Children at High Risk of Progression to Severe COVID-19 *Aged ≥28 Days to <12 Years* • Remdesivir (Veklury) o ≥3 to <40 kg: Lyophilized powder only; IV loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose once daily on Days 2 and 3	Non-hospitalized Children at High Risk of Progression to Severe COVID-19 *Aged ≥28 Days to <12 Years* • N/A *Aged ≥12 Years* • Remdesivir (Veklury) o ≥3 to <40 kg: Lyophilized powder only, IV: loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose	Remdesivir is administered intravenously. When given to non-hospitalized patients, duration is for 3 days. When given to hospitalized patients, duration is generally 5 days or until hospital discharge, whichever is first, but may extend to up to 10 days based on clinical response. Remdesivir should be started within 7 days of symptom onset but could be considered if presenting with >7 days of symptoms in children with severe immunosuppression. Ritonavir-boosted nirmatrelvir is an oral PI that may be administered with other ARVs, including those that contain ritonavir or cobicistat, without any interruption or modification to the usual ART. However, there is potential for significant drug–drug

Indication	First Choice	Alternative	Comments/Special Issues
	○ ≥40 kg: Injection solution or lyophilized powder; IV loading dose: 200 mg on Day 1, followed by 100 mg once daily on Days 2 and 3 *Aged ≥12 Years and ≥40 kg* • Nirmatrelvir 300 mg and ritonavir 100 mg, administered together (Paxlovid), twice daily for 5 days Hospitalized Children • Remdesivir (Veklury) ○ ≥3 to <40 kg: Lyophilized powder only; IV loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose once daily on Days 2 through 5 ○ ≥40 kg: Injection solution or lyophilized powder; IV loading dose: 200 mg on Day 1, followed by 100 mg once daily on Days 2 through 5 • Dexamethasone 0.15 mg/kg (with a maximum dose of 6 mg), oral or IV, once daily for up to 10 days	once daily on Days 2 and 3 ○ ≥40 kg: Injection solution or lyophilized powder, IV: loading dose: 200 mg on Day 1, followed by 100 mg once daily on Days 2 and 3	interactions with other medications, requiring dose or frequency adjustment or avoidance. Consult a drug interactions database, such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance. Ritonavir-boosted nirmatrelvir should be started within 5 days of symptom onset. Renal and hepatic function should be evaluated prior to initiating ritonavir-boosted nirmatrelvir, and doses should be adjusted if needed. Dexamethasone has potential for drug–drug interactions, including with NNRTIs. Providers should consult a drug interactions resource, such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance. Alternative corticosteroids, such as hydrocortisone or methylprednisolone, may be considered if dexamethasone is not available or if alternative corticosteroids are being administered for another indication.

Key: ART = antiretroviral therapy; ARV = antiretroviral drug; CDC = Centers for Disease Control and Prevention; IV = intravenous; NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitor

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

Panel's Recommendations

- Routine use of antifungal medications is not recommended for primary prophylaxis of cryptococcal infections in children **(BIII)**.
- Combination therapy with amphotericin B deoxycholate (or liposomal amphotericin B) and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for central nervous system disease **(AI*)**. Amphotericin B lipid complex is another alternative to amphotericin B deoxycholate **(BII*)**
- Liposomal amphotericin B is preferred over amphotericin B deoxycholate for patients with or at risk of renal insufficiency **(AI*)**; amphotericin B lipid complex is an alternative **(BII*)**.
- In patients who cannot tolerate flucytosine or if flucytosine is unavailable, amphotericin B deoxycholate (or liposomal amphotericin B or amphotericin B lipid complex) with or without high-dose fluconazole can be used for initial therapy **(BI*)**. Fluconazole plus flucytosine is superior to fluconazole alone and an option in patients who cannot tolerate any form of amphotericin **(BII*)**.
- Echinocandins are not active against cryptococcal infections and should not be used **(AIII)**.
- After a minimum of 2 weeks of induction therapy, if there is clinical improvement and a negative cerebrospinal fluid culture after repeat lumbar puncture, amphotericin B and flucytosine can be discontinued and consolidation therapy with fluconazole administered for a minimum of 8 weeks **(AI*)**; itraconazole is a less preferable alternative to fluconazole **(BI*)**.
- Secondary prophylaxis with fluconazole **(AI*)** or itraconazole (less preferable) **(BI*)** is recommended for a minimum of 1 year.
- Discontinuing secondary prophylaxis (after receiving secondary prophylaxis for ≥ 1 year) can be considered for asymptomatic children aged ≥6 years with CD4 counts ≥100 cells/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: • Documented disease Criteria For Discontinuing Secondary Prophylaxis *If **All** of the Following Criteria are Fulfilled:* • Age ≥6 years • Asymptomatic on ≥12 months of secondary prophylaxis • CD4 count ≥100 cells/mm^3 with undetectable HIV viral load on cART for >3 months Criteria for Restarting Secondary Prophylaxis: • CD4 count <100/mm^3
Treatment	CNS Disease *Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy):* • 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 *Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)* *If Flucytosine Not Tolerated or Unavailable:* • **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. 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.

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

Indication	First Choice	Alternative	Comments/Special Issues
Treatment, continued	*Consolidation Therapy (Followed by Secondary Prophylaxis):* • 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:* • 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 *Consolidation Therapy (followed by secondary prophylaxis):* • 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. Liposomal amphotericin and amphotericin B lipid complex are **significantly more expensive than amphotericin B deoxycholate**. 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]: • 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)[b]: • Amphotericin B, 0.7–1.0 mg/kg body weight, or • Amphotericin liposomal 3–5 mg/kg body weight, or • Amphotericin lipid complex, 5 mg/kg body weight IV once daily	Serum itraconazole concentrations should be monitored to optimize drug dosing. Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake, or impair its renal excretion, or both. Flucytosine dose should be adjusted to keep 2-hour post-dose drug levels at 40–60 µg/mL
	Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[b]: • Amphotericin B 0.7–1.0 mg/kg body weight, or • Liposomal amphotericin, 3–5 mg/kg body weight, or • Amphotericin B lipid complex 5 mg/kg body weight IV once daily (± flucytosine)	Disseminated disease (CNS not involved) or severe, pulmonary disease[b]: • 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	Oral acetazolamide **should not** be used for reduction of ICP in cryptococcal meningitis. Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis. 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

Updated: August 29, 2019
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 *Strength of Recommendation: Strong; Weak* *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 ≤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/mm^3, 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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Dosing Recommendations for Prevention and Treatment of Cryptosporidiosis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	ARV therapy to avoid advanced immune deficiency	N/A	N/A
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	Effective ART • 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. Nitazoxanide • 1–3 years of age: Nitazoxanide (20 mg/ mL oral solution) 100 mg orally twice daily with food • 4–11 years of age: Nitazoxanide (20 mg/ mL oral solution) 200 mg orally twice daily with food • ≥12 years of age: Nitazoxanide tablet 500 mg orally twice daily with food *Treatment Duration* • 3–14 days	Supportive Care • Hydration, correct electrolyte abnormalities, nutritional support Antimotility agents (such as loperamide) should be used with caution in young children.

Key: ARV = antiretroviral; ART = antiretroviral therapy

Cytomegalovirus

Updated: August 3, 2023
Reviewed: August 3, 2023

Panel's Recommendations
I. Is there an indication for cytomegalovirus (CMV) antibody testing in children with asymptomatic HIV (versus not testing) to guide clinical management?
• CMV antibody testing is recommended at age 1 year (or at baseline evaluation if age >1 year at initial visit) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 T lymphocyte [CD4] cell count <100 cells/mm^3 or CD4 percentage <10%) (strong, low).
II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not screening)?
• Testing for congenital CMV infection in the first 21 days of life is recommended for infants with vertically transmitted HIV (strong, low). CMV testing is also suggested for all infants exposed to HIV since their HIV status will be indeterminate during the first 21 days of life when congenital CMV infection can be diagnosed (weak, low). Infants with confirmed congenital CMV infection should be evaluated regularly for early detection of hearing loss and appropriate intervention.
III. Is primary prophylaxis against CMV recommended for children with HIV who are CMV-seropositive (versus not providing prophylaxis)?
• Primary prophylaxis against CMV disease is not recommended for children with HIV who are not severely immunocompromised (strong, moderate). CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 count >100 cells/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 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 CD4 percentage >10% in children <6 years (weak, low).
IV. In CMV-seropositive children with HIV age <5 years, is routine ophthalmologic examination recommended to screen for CMV retinitis (versus not providing routine ophthalmologic examination)?
• Children with HIV aged <5 years who are CMV infected and severely immunosuppressed (i.e., CD4 count <50 cells/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.
V. Among children with HIV and CMV disease, is treatment with anti-CMV antiviral agents in addition to ART (versus ART alone) associated with higher rates of remission, decreased mortality, or both?
• Treatment with antiviral therapy against CMV in addition to ART is recommended for CMV disease in children with HIV (strong, moderate). Intravenous (IV) ganciclovir is the drug of choice for initial treatment for acquired CMV disease, including retinitis and other end-organ disseminated CMV disease (e.g., colitis, esophagitis, and CNS disease). Transition from IV ganciclovir to oral valganciclovir can be considered for patients who improve on IV therapy (strong, moderate).
• Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV (strong, moderate).
• Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease (weak, very low).

Panel's Recommendations
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 recommendation is based on studies among children with symptomatic congenital CMV infection but without HIV. VI. Is secondary prophylaxis after treatment of CMV disease (versus no secondary prophylaxis) recommended in severely immunocompromised children with HIV? • After induction therapy, secondary prophylaxis (chronic maintenance therapy) is recommended for most forms of CMV disease until immune reconstitution or, in the absence of immune reconstitution, for the remainder of a patient's life. Regimens for chronic suppression include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir (strong, moderate). • Secondary prophylaxis (chronic maintenance therapy) is not routinely recommended for CMV gastrointestinal disease but should be considered if relapses occur (expert opinion). A role for secondary prophylaxis (maintenance therapy) for CMV pneumonitis also has not been established. VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children with HIV who have well-controlled HIV (versus continuation of secondary prophylaxis)? • Discontinuation of secondary prophylaxis may be considered for children who are receiving ART and have a sustained (e.g., >6 months) increase in CD4 count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 count to >100 cells/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).
Rating System *Strength of Recommendation: Strong or Weak* *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 woman 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 women 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 • 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— • 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). Criteria for Discontinuing Primary Prophylaxis • Age ≥6 years with CD4 count >100 cells/mm^3 • Age <6 years with CD4 percentage >10% Criteria for Considering Restarting Primary Prophylaxis • Age ≥6 years with CD4 count <50 cells/mm^3 • Age <6 years with CD4 percentage <5%
Secondary Prophylaxis	• Ganciclovir 5 mg/kg body weight IV once daily, or • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food, or • 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 • 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— • Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse. Criteria for Discontinuing Secondary Prophylaxis (All of the Following Criteria Must Be Fulfilled) • Completed ≥6 months of ART • Age <6 years with CD4 percentage ≥15% for >6 consecutive months • Age ≥6 years with CD4 count >100 cells/mm^3 for >6 consecutive months • Consultation with ophthalmologist (if retinitis) 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 • Age <6 years with CD4 percentage <15% • Age ≥6 years with CD4 count <100 cells/mm^3
Treatment	Symptomatic Congenital Infection • 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 Disseminated Disease and Retinitis *Induction Therapy* • 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) *Chronic Maintenance Therapy* • Ganciclovir 5 mg/kg body weight once daily for 5–7 days Central Nervous System Disease *Induction Therapy* • 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 *Induction Therapy* • 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 *Chronic Maintenance Therapy* • Foscarnet 90–120 mg/kg body weight IV once daily *Alternative Therapy for Retinitis (Followed by Chronic Maintenance Therapy; See Secondary Prophylaxis)* • Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above). 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. • 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. • 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. Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children. 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. 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 • 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

Updated: August 29, 2019
Reviewed: August 29, 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 $\leq$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 by mouth, administered as one dose given with food (maximum 2 g). Note: Based on data from children who are HIV-negative • Nitazoxanide. o 1–3 years: Nitazoxanide 100 mg by mouth every 12 hours with food for 3 days o 4–11 years: Nitazoxanide 200 mg by mouth every 12 hours with food for 3 days o ≥12 years: Nitazoxanide 500 mg by mouth every 12 hours with food for 3 days 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. 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. Supportive Care • Hydration • Correction of electrolyte abnormalities • Nutritional support 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 Infection

Updated: June 05, 2025
Reviewed: June 05, 2025

These recommendations are intended to focus on prepubertal children with HIV and hepatitis B virus (HBV) coinfection.

Panel's Recommendations
I. Should all pregnant women with HIV routinely undergo testing for hepatitis B virus (HBV) as part of antenatal care? All pregnant women with HIV should be tested for HBV with hepatitis B surface antigen (HBsAg) as part of the pregnancy/obstetric panel during the first trimester of each pregnancy regardless of hepatitis B (HepB) vaccination history or prior testing. Testing should be repeated in late pregnancy or at the time of admission to the hospital for infant delivery for HBsAg-negative people at high risk of HBV infection (e.g., people who inject drugs, have intercurrent sexually transmitted infections, have multiple sex partners, or have clinical hepatitis). Pregnant women with HIV who do not have documentation of HepB vaccination should be vaccinated against hepatitis B (**strong**, **moderate**). Pregnant women who are HBsAg positive should also have an HBV DNA quantitative test and a hepatitis B e antigen (HBeAg) test and be referred to appropriate specialists for hepatitis B–related clinical management; HBV specialists can ensure essential follow-up of the pregnant woman and the hepatitis B–exposed infant(s), as well as provision of HepB vaccines for sexual and household contacts. Prevention of hepatitis B in newborn infants relies on providing a birth dose (within 12 hours after birth is optimal) of the HepB vaccine to all infants. In addition to HepB vaccine, infants born to women known to be HBsAg positive should receive hepatitis B immune globulin (HBIG) within 12 hours of birth. Infants born to women with unknown HBsAg status should receive HepB vaccine within 12 hours of birth in conjunction with HBIG provided within 12 hours of birth (for infants <2,000 grams) or within 7 days (for infants ≥2,000 grams) unless the pregnant woman is confirmed to be HBsAg negative by this time. When indicated, HBIG should be administered concurrently with the birth dose of HepB vaccine at a different anatomic site. Infants born to women who are HBsAg negative but who have other evidence of HBV infection (e.g., detection of HBV DNA HBeAg-positive, or known chronic HBV infection) should be managed as though they have been born to HBsAg-positive women. See Hepatitis B Virus/HIV Coinfection in the Perinatal Guidelines for more information.
II. What is the optimal antiretroviral (ARV) regimen for people with HIV/HBV coinfection in the antenatal period? Antiretroviral therapy (ART) that is active against both HIV and HBV is recommended; the preferred regimen should include tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and either lamivudine (3TC) or emtricitabine (FTC) (**strong**, **high**). See Hepatitis B Virus/HIV Coinfection in the Perinatal Guidelines for more information.
IIIa. What is the optimal HBV prevention strategy for infants born to women with HIV/HBV coinfection? All infants ≥2,000 grams born to HBsAg-positive women should receive single-antigen HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 to 2 months, and a third dose of HepB vaccine at age ≥6 months. All infants <2,000 grams born to HBsAg-positive women should receive single-antigen HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 month, a third dose of HepB vaccine at age 2–3 months, and a fourth dose of HepB vaccine at age ≥6 months and not before 24 weeks (**strong**, **high**). See Hepatitis B Virus/HIV Coinfection in the Perinatal Guidelines for more information.
IIIb. What is the optimal initial HepB vaccination strategy for children with HIV? Children with HIV should receive a standard dose of HepB vaccine at 0, 1, and 6 months (**strong**, **high**). A double dose at 0, 1, and 6 months may also be considered (**weak**, **moderate**).

IV. When should infants born to women with HIV/HBV coinfection undergo post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Infants born to women with HIV/HBV coinfection should have serologic testing for antibody to hepatitis B surface antigen (anti-HBs) and HBsAg at age 9 to 12 months (i.e., the next well-child visit after completion of the HepB vaccine series) or 1 to 2 months after completion of the vaccine series if the final dose is delayed to assess for vaccine response and failure of perinatal prophylaxis (strong, moderate).

V. When should children and adolescents with HIV have post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Due to the high prevalence of HBV infection, all infants, children, and adolescents with HIV should be tested for HBsAg as soon as possible after HIV diagnosis (strong, high). If there is no documentation of routine infant/child vaccination for hepatitis B, initial screening with the triple panel consisting of HBsAg, anti-HBs, and total antibody to hepatitis B core antigen (anti-HBc) will determine infection and immune status and guide clinical management. In addition, individuals with the isolated anti-HBc serologic profile should also be vaccinated for hepatitis B.

Anti-HBs titers should be evaluated 4 to 6 weeks after completion of the vaccination series (strong, moderate). See Advisory Committee on Immunization Practices' (ACIP) recommendations on eliminating transmission of HBV infection and preventing HBV infection for more information.

VI. What is the best strategy for HepB revaccination of children with HIV who have not responded to the primary HepB vaccine series (anti-HBs <10 mIU/mL)?

If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, the Panel on Opportunistic Infections in Children With and Exposed to HIV now recommends that children should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs remains <10 mIU/mL following single-dose revaccination should receive two additional doses of HepB vaccine to complete the second series, followed by postvaccination serologic testing 1 to 2 months after the final dose. Alternatively, based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete three-dose series, followed by postvaccination serologic testing performed 1–2 months after the final dose of vaccine (strong, moderate). See ACIP's HBV immunization strategy for more information.

VII. Should individuals with HIV who have responded to HepB vaccination have ongoing assessment of hepatitis B immunity?

In individuals who respond to HepB vaccination (anti-HBs ≥10 mIU/mL), periodic assessment of anti-HBs titers can be considered every 5 years. A booster dose should be provided if anti-HBs titer falls below 10 mIU/mL. Anti-HBs titers should be checked 4 to 6 weeks after a booster dose (weak, very low). If anti-HBs is still <10 mIU/mL, the standard three-dose series should be completed. See ACIP's recommendations on hepatitis B prevention for more information.

VIII. What ART regimens should be considered for ARV-naive children with HIV/HBV coinfection who are immunotolerant to HBV?

- For children aged <2 years, a standard preferred ART regimen should be provided. Although there is a risk for development of 3TC-resistant HBV, the need to provide optimal HIV therapy outweighs this risk (strong, high).
- For children aged ≥2 years to <12 years, a standard preferred ART regimen should be provided. If feasible (weight ≥14 kg), the ART regimen should include TDF (or TAF) + 3TC or FTC (strong, low).
- For children aged ≥12 years, a standard preferred ART regimen including TDF (or TAF) + 3TC or FTC should be provided (strong, low).

IX. Should 3TC or FTC be the only HBV therapy for children with HIV/HBV coinfection who require treatment of both infections?

- Children with HIV/HBV coinfection who require treatment of both infections should not be treated with 3TC or FTC as the only HBV-active agent in the regimen (strong, moderate). In addition to 3TC or FTC, inclusion of tenofovir (TDF or TAF) in the ART regimen is recommended for most children with HIV/HBV coinfection.

X. What treatment regimens should be considered for children with HIV/HBV coinfection who require treatment of both infections?

- For children aged ≥2 years who require treatment for both infections, a combination ARV regimen that includes TDF (or TAF) and an anti-HBV nucleoside (either 3TC or FTC) should be considered for treatment (strong, low).
- For children aged ≥2 years, if TDF (or TAF) is not available or not tolerated, entecavir can be added to a fully suppressive ARV regimen for HBV treatment (weak, low).

XI. How often should children with HIV/HBV coinfection be monitored for HBV status and disease activity?

Children with HIV/HBV coinfection who are not receiving HBV-directed treatment should have disease monitoring (alanine aminotransferase [ALT] for inflammation, complete blood count for platelet count and leukopenia, HBeAg/anti-HBe serostatus, HBV DNA, and HBsAg/anti-HBs serostatus) like children with HBV mono-infection (strong, moderate). The value of intermittent noninvasive assessment of hepatic fibrosis with such techniques as transient elastography is unclear (see the Phases of Chronic Hepatitis B Infection table).

XII. How should children with HIV/HBV coinfection be monitored for hepatocellular carcinoma?

There is no difference in screening recommendations for hepatocellular carcinoma (HCC) in children with HIV/HBV infection compared to children with HBV mono-infection. Surveillance of chronic HBV infection using abdominal ultrasound every 6 months should be performed to detect early HCC in people at risk: people with cirrhosis and those with HBsAg positivity without cirrhosis but with active hepatitis or family history of HCC. Children with a lower risk of HCC should be screened every 1 to 2 years with alpha-fetoprotein (AFP) and every 1 to 2 years with ultrasound, or sooner if AFP is >10 mcg/mL (weak, low).

XIII. How should children with HIV who are anti-HBc positive be monitored for reactivation of HBV infection?

Children with HIV who are anti-HBc positive are at risk for reactivation of HBV infection if HIV-related immunodeficiency worsens or if they are treated with agents associated with a risk of HBV reactivation (cancer chemotherapy, biologics such as anti-tumor necrosis factor-alpha, and direct-acting antivirals [DAAs] for hepatitis C curative treatment). For children initiating rituximab or other B-cell–depleting agents who are not on HBV-active ART, HBV antiviral therapy should be initiated. For children experiencing worsening HIV-related immunodeficiency or who are receiving cancer chemotherapy or high-dose steroids, periodic ALT and HBV DNA monitoring should be considered. For children receiving DAAs for hepatitis C curative treatment, HBsAg-positive children should receive prophylactic HBV treatment as part of HIV ART, and HBV DNA should be assessed at regular intervals to monitor for hepatotoxicity (weak, very low).

Rating of Evidence

Strength of Recommendation: Strong; Weak

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

Epidemiology

Hepatitis B virus (HBV) is a DNA virus that causes both acute and chronic hepatitis and is associated with an increased risk of hepatocellular carcinoma (HCC). Transmission is via exposure to bodily fluids from individuals with HBV infection. This guideline will focus on the issues related to children and prepubertal adolescents with or at risk for HIV/HBV coinfection. The reader is referred to recent reviews and guidelines on HBV infection in populations without HIV[1-9] and in sexually mature adolescents and adults with HIV.[10,11]

HBV infection is a common worldwide infection for which prevalence varies from <1% in the United States and Europe to as much as 10% to 15% in areas of Africa, Southeast Asia, and Eastern Europe. However, prevalence in low- and middle-income countries is likely underestimated due to issues with diagnosis.[12] In 2022 there were an estimated 1.2 million new infections with HBV.[12]

Chronic HBV infection is often defined as persistence of serum hepatitis B surface antigen (HBsAg) for >6 months.[13] The risk of developing chronic HBV infection after acute infection correlates inversely with age and immune competence at HBV exposure. Chronic HBV infection following acute 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.[7,14-18]

Infants and children most commonly acquire HBV infection perinatally or through postnatal household contact, particularly in areas of high HBV endemicity.[19-21] HBV can also be acquired parenterally or through sexual transmission. Pregnant women with HIV/HBV coinfection can transmit HIV, HBV, or both perinatally; it is not known if maternal HIV coinfection modifies the risk of HBV perinatal transmission.[22] Maternal HBV infection is not a contraindication to breastfeeding. Horizontal transmission of HBV can occur through interpersonal contact between non-intact skin or mucous membranes and blood or body fluids that contain HBV (e.g., injuries, wounds) or through sharing personal-care objects (e.g., toothbrushes, razors). Universal hepatitis B (HepB) 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.[23] The risk from blood transfusions in countries with blood bank screening is estimated to be very low (1.37 per million donations).[24]

Prevention of HBV transmission at birth among perinatally exposed infants is very effective.[25] A three-dose HepB vaccine regimen is 70% to 95% effective in preventing HBV infection in infants exposed to HBV and is 85% to 95% effective when combined with hepatitis B immune globulin (HBIG).[26] The level of antibody to hepatitis B surface antigen (anti-HBs) considered protective is ≥10 mIU/mL. There is an increased risk of perinatal transmission if the pregnant woman has a high circulating level of HBV DNA.

The local prevalence of HBV/HIV coinfection in children and adolescents varies widely; from 1% in one study of 371 transfused children in the Democratic Republic of Congo, to 45% in a study of 179 Romanian children with HIV diagnosed before 16 years of age, not due to perinatal transmission.[27,28] Regional variation in the prevalence of HIV/HBV coinfection is the major determinant of risk to children from different regions. In the National Health and Nutrition Examination Survey, 2001 through 2018, the estimated antibody to hepatitis B core antigen (anti-HBc) prevalence among United States–born people aged 6 to 29 years was 0.7% (95% confidence interval [CI], 0.5% to 1.0%) during 2001 to 2006, 0.7% (95% CI, 0.5% to 1.0%) during 2007 to 2012, and 0.5% (95% CI, 0.3% to 0.8%) during 2013 to 2018.[29] A small case series among children with HIV at an urban hospital in the United States reported a 2.6% chronic HBV prevalence in 228 children with HIV.[30] A study of chronic HBV infection in children with HIV in Senegal reported a prevalence of 4.1% among 613 children.[31]

Most children who acquire HBV perinatally are initially immunotolerant to HBV (see Phases of Chronic HBV Infection for definitions) and may remain immunotolerant with chronic infection 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.[8,32]

Clinical Manifestations

Most acute HBV infections in children are asymptomatic.[32] 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 children with HBV infection include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. However, rare cases of acute hepatic failure have occurred during perinatal and childhood HBV infection.[33,34]

Similar to children with isolated HBV infection, most children with HIV and chronic HBV infection do not experience HBV-related symptoms related. Infants and children with chronic HBV are at an increased risk of developing cirrhosis or HCC over the course of their life, which is dependent on HBV genotype and other factors.[35,36] However, these sequelae usually develop over two to three decades and rarely occur during childhood.[37,38] Development of HCC correlates with HBV DNA levels, HBV genotype, and duration of HBV infection, with the highest risk in people infected in early life.[39] There are no data on HCC outcomes in children with HIV/HBV coinfection. However, adults with HIV/HBV coinfection are at increased risk of cirrhosis, end-stage liver disease, and liver-related mortality.[11,40,41]

In people with HIV/HBV coinfection starting combination antiretroviral therapy (ART), serum transaminase elevations (flares) can occur as part of immune reconstitution inflammatory syndrome (IRIS)[42] or secondary to ART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune-mediated, and restoration of immunocompetence with antiretroviral (ARV) treatment may reactivate liver inflammation and damage. Initiation of ART without anti-HBV therapy can lead to reactivation of HBV. This does not represent a failure of ART but rather a sign of immune reconstitution. IRIS manifests by an increase in serum transaminase levels as the CD4 T lymphocyte (CD4) cell count increases during the first 6 to 12 weeks of ART. Thus, serum transaminase levels should be monitored closely after introduction of ART. In such situations, ART should be continued and treatment for HBV infection initiated if it is not included in the ART (see Treatment Recommendations below). The prognosis in individuals with IRIS is generally favorable because a robust inflammatory response may predict an excellent response to ART in terms of immune reconstitution, and perhaps, improved survival.[43] In people 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 an HIV specialist with a specialist in hepatic disease is recommended for such scenarios; a hepatologist should be consulted promptly if elevated aminotransferase levels are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

Diagnosis

All children with a new HIV diagnosis should be tested for HBV infection,[44] as the HBV status could impact ARV management and monitoring.[44]

HBsAg is the first detectable serologic marker, appearing 30 days after HBV infection; HBsAg precedes the elevation of serum aminotransferase levels and the onset of symptoms. Necroinflammatory liver disease can then occur, during which serum transaminase levels increase, along with high HBV DNA levels and hepatitis B e antigen (HBeAg) positivity.

HBeAg correlates with viral replication, DNA polymerase activity, infectivity, and increased severity of liver disease.

Serologic Markers for HBV

HBsAg (Hepatitis B Surface Antigen)

- **Self-limited infections:** Usually eliminated in 1 to 2 months
- **Chronic infections:** Persistently positive beyond 6 months, with no detectable anti-HBs in individuals who have never been vaccinated

Anti-HBc (Antibody to Hepatitis B Core Antigen) Immunoglobulin M

- Appears **1 to 2 weeks after HBsAg**[25]

Anti-HBc Immunoglobulin G (IgG)

- **Persists for life**
- **Passively transferred maternal anti-HBc IgG:** Detectable in infants up to 24 months after birth[25]

Anti-HBs (Antibody to Hepatitis B Surface Antigen)

- Develops during **convalescence** in self-limited infections
- **Indicates immunity** from HBV infection
- **Post–recovery from natural infection:** Both anti-HBs and anti-HBc IgG are present.
- **Postvaccination without prior infection:** Detectable anti-HBs but no anti-HBc or HBsAg.
- **Inadvertent vaccination after recovery from HBV infection:** Detectable anti-HBs and anti-HBc upon postvaccination testing. (See Table 1 from the Advisory Committee on Immunization Practices' (ACIP) Recommendations on Hepatitis B Immunization for review of interpretation of serologic test results for HBV infection.)

HBV Reactivation

- Despite immunity, HBV can be incorporated into the human genome and reactivate if a person becomes immunocompromised.[45]

There are four recognized phases of chronic HBV infection. For individuals with chronic HBV infection, HBeAg seroconversion (defined as loss of HBeAg followed by HBeAg antibody [i.e., anti-HBe] production) usually marks the transition to the inactive carrier state, also known as chronic carrier state, where HBsAg remains positive. However, some people 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 HBeAg seroconversion is very infrequent in children aged <3 years.[15,46] 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.[37] HBeAg seroconversion usually is followed by a reduction in serum HBV DNA levels and an initial increase and then subsequent normalization of serum

transaminase levels, followed by resolution of necroinflammatory liver disease.[37] HBeAg seroconversion rates have not been reported for children with HIV/HBV coinfection. Development of cirrhosis and HCC is more common in patients with delayed HBeAg seroconversion.[47] HBeAg-negative infection (pre-core mutant) is uncommon in children.[48]

HBV DNA is a marker for HBV replication. The immunotolerant phase is characterized by high levels of HBV replication without evidence of active liver disease. In the immunoactive phase of chronic HBV, high HBV DNA levels have been associated with necroinflammatory liver disease. Children who acquired HBV perinatally, however, may remain in an immunotolerant phase with high levels of HBV DNA without evidence of liver damage and with 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 or transient elastography may be useful to assess the degree of liver damage and determine the need for treatment.[49,50]

Phases of Chronic HBV Infection

State	HBeAg/Anti-HBe	HBV DNA[a]	ALT
Immunotolerant	Positive/Negative	>1,000,000 IU	Normal
Immunoactive	Positive/Negative	>20,000 IU	Elevated
Chronic Carrier	Negative/Positive	<2,000 IU	Normal
HBeAg-Negative Hepatitis	Negative/Positive	>10,000 IU	Elevated

[a] Values are the typical ranges but can vary in specific patients.

Key: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus

General Management Considerations

Children with HBV infection should be advised not to share toothbrushes or other personal-care articles that may be contaminated with blood (e.g., razors, tweezers, nail clippers) and to cover open or draining wounds.[9] Safe sex practices should be encouraged for all sexually active adolescents and young adults with HIV; barrier precautions (e.g., latex condoms) are recommended to reduce the risk of exposure to sexually transmitted pathogens, including HBV. All children should receive hepatitis A (HepA) vaccination at age 12 to 23 months, with the two doses in the series administered at least 6 months apart.[51] Children who are not fully vaccinated by age 2 years can be vaccinated at subsequent visits. The HepA vaccine is also recommended for children and adolescents aged ≥24 months who were not previously vaccinated; see the Immunizations for Preventable Diseases in Children and Adolescents With HIV section.[25] International travelers aged 6 months through 11 months are recommended for HepA vaccine if traveling internationally to areas endemic or epidemic for hepatitis A. Children and adolescents with HBV should be screened for hepatitis C virus (HCV) infection. Household contacts should have their HepB vaccination status reviewed and updated if they have not been vaccinated.

Prevention Recommendations

Preventing Exposure

I. Should all pregnant women with HIV routinely undergo testing for hepatitis B as part of antenatal care?

All pregnant women with HIV should be tested for HBV infection with HBsAg, anti-HBc, and anti-HBs during an early prenatal visit. Testing for HBsAg should be repeated in late pregnancy for HBsAg-negative people who are at high risk of HBV infection (e.g., people who inject drugs, people with intercurrent sexually transmitted infections, people with multiple sex partners). Pregnant women who do not have documentation of HepB vaccination, immunity to, or infection with HBV should be vaccinated against hepatitis B **(strong, moderate).** Evidence suggests that people with HIV are at equal or increased risk for infection with HBV compared to people without HIV.[52,53] Multiple clinical guidelines, including the Perinatal Guidelines, have addressed this issue.[2,54]

Pregnancy is not a contraindication or precaution to HepB vaccination for people who have not previously been vaccinated; current HepB vaccines contain noninfectious HBsAg and should cause no risk to the fetus. Pregnant women who are identified as at risk of HBV infection during pregnancy should be promptly vaccinated.[55] Providers should vaccinate pregnant women needing HepB vaccination with Engerix-B, Heplisav-B, Recombivax HB, or Twinrix.[56]

Preventing Disease

II. What is the optimal ARV regimen for people with HIV/HBV coinfection in the antenatal period?

ART active against both HIV and HBV is recommended; the preferred regimen should include tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and either lamivudine (3TC) or emtricitabine (FTC) **(strong, high).**

Studies in HIV/HBV coinfection are sparse, but one small study of 35 pregnant women with HIV/HBV coinfection demonstrated a numerically higher proportion of women with undetectable HBV viral load at delivery in those who received TDF/3TC (11 of 15 participants; 73%) compared to 3TC alone (8 of 16 participants; 50%) ($P = 0.27$).[57] Studies in women with HBV mono-infection demonstrate that TDF and TAF, both approved by the U.S. Food and Drug Administration for HIV and HBV infection, can reduce HBV perinatal transmission.[58,59] See Intrapartum Care for People With HIV in the Perinatal Guidelines for more details on prevention of HBV transmission in pregnant women with HIV/HBV coinfection.

IIIa. What is the optimal HBV prevention strategy for infants born to women with HIV/HBV coinfection?

All infants born to HBsAg-positive people should receive HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 to 2 months, and a third dose at age ≥6 months but not before 24 weeks (see text below for adjustments for infants <2,000 grams) **(strong, high).** Infants who test negative for HIV and who do not have a response on postvaccination serologic testing (see Question IV below) to the initial vaccine series may receive a challenge dose. If the anti-HBs titer is ≤10 mIU/mL, then revaccination with the standard series should be performed.

The initial recommendation for vaccination of infants born to women with HIV/HBV coinfection is not different from the initial recommendation for infants born to women with HBV mono-infection (Figure 1).[25,54] See Hepatitis B Virus/HIV Coinfection in the Perinatal Guidelines for more information. In preterm infants weighing <2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of HepB vaccine in these infants. Therefore, three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches 1 month of age.[60] In addition, term (birth weight ≥2,000 g) and preterm (birth weight <2,000 g) infants born to women with HIV whose HBsAg status is unknown at delivery should receive the first dose of HepB vaccine within 12 hours of birth. Infants weighing <2,000 g should also receive HBIG within 12 hours of birth. Pregnant women with HIV and unknown HBsAg status should be tested as soon as possible. If the pregnant woman is determined to be HBsAg positive, infants weighing ≥2,000 grams should also receive HBIG as soon as possible but no later than age 7 days. The three-dose series of HepB vaccine is also recommended for *all* children and adolescents with HIV who were not previously vaccinated **(strong, high).**

All infants >2,000 grams born to women with HIV who are HBsAg negative should also receive the HepB vaccine series, with a first dose administered during the birth hospitalization, a second dose at age 1 to 2 months, and a third dose at 6 to 18 months of age.[60-62] Dosing adjustments for infants ≤2,000 grams as detailed above are similarly recommended. **(strong, high).** The third dose must be given at 24 weeks or after. The minimal interval between vaccine doses are 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3. Although longer intervals in the last two doses result in higher antibody levels, following minimum intervals is recommended, as longer intervals may increase the risk of infection in those who have a delayed response to vaccination.[63]

IIIb. What is the optimal initial vaccination strategy in children with HIV?

Children with HIV should receive a standard dose of HepB vaccine at 0, 1, and 6 months **(strong, high).** A double dose at 0, 1, and 6 months may also be considered **(weak, moderate).**

Children with HIV should receive the HepB vaccine series. Two randomized trials have evaluated different strategies of vaccination, with the standard dose at 0, 1, and 6 months, demonstrating response rates of 60% to 92%.[64,65] Individuals with higher CD4 counts and HIV viral suppression are more likely to have a vaccine response. In another randomized controlled trial, higher dose of HepB vaccine or use of Twinrix (combination HepA/HepB vaccine) had a higher response rate in children with HIV compared to standard dose of HepB vaccine.[66]

IV. When should infants born to women with HIV/HBV coinfection undergo post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Infants born to women with HIV/HBV coinfection should have anti-HBs and HBsAg testing performed at age 9 to 12 months or 1 to 2 months after completion of the vaccine series if the final dose is delayed **(strong, moderate)** to assess for vaccine response and failure of perinatal prophylaxis.

Recent data in infants born to women without HIV has shown that the optimum time for postvaccination testing is 1 to 2 months after the last dose of a three-vaccine series.[67,68] Testing for vaccine response should not be performed prior to 9 months of age to avoid detection of anti-HBs from neonatally administered HBIG.[60] Similar testing should be performed on children with HIV

who receive their primary HepB vaccination later. One study suggests that there is a lower response rate to HepB vaccination in HIV-exposed infants compared to non-HIV-exposed infants.[69]

V. When should children and adolescents with HIV have post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Due to the intermediate to high prevalence of HBV infection in people with HIV infection and clinical management implications, all infants, children, and adolescents with HIV should be tested for HBsAg as soon as possible after HIV diagnosis **(strong, high).**

In children and adolescents with HIV who receive HBV vaccination, anti-HBs testing should be performed 4 to 6 weeks after completion of the vaccine series **(strong, moderate).**

The reasoning for this testing schedule is similar to the reasoning behind the testing schedule for infants.[68] No data in individuals with HIV indicate a more delayed response to HepB vaccination. Response rates to HepB vaccination as determined by anti-HBs titers of >10 mIU/mL at 4 to 6 weeks after the last dose of vaccine have been reported to be between 29% and 71%.[70-72] Antibody responses to HepB vaccination may be diminished in children with HIV,[73] especially in older children, children with CD4 counts <200 cells/mm^3, or children with higher HIV viral loads.[74-76]

VI. What is the best strategy for HBV revaccination of children with HIV who have not responded to the primary HepB vaccine series (anti-HBs <10 mIU/mL)?

If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, the Panel on Opportunistic Infections in Children With and Exposed to HIV (the Panel) now recommends that children should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs remains <10 mIU/mL following single-dose revaccination should receive two additional doses of HepB vaccine to complete the second series, followed by postvaccination serologic testing 1 to 2 months after the final dose. Alternatively, based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete three-dose series, followed by postvaccination serologic testing performed 1 to 2 months after the final dose of vaccine **(strong, moderate).** See ACIP's HBV immunization strategy for more information. There are no randomized controlled trials of HBV revaccination strategies for children with HIV who had a nonresponse to the primary HepB vaccination series. A single booster vaccination only resulted in a 37% rate of protective antibody at 8 weeks in one study[77] and a 50% rate in another.[78] In contrast, several studies of revaccination with a second series demonstrated protective responses (anti-HBs titer >10 mIU/mL) in 52% to 92% of children, adolescents, and adults with HIV.[79-83] One prospective trial of 63 Thai children with HIV on ART who were HepB vaccine nonresponders demonstrated that revaccination with a standard dose (10 mcg of recombinant vaccine) at 0, 2, and 6 months resulted in 92% of participants having anti-HBs titers ≥10 mIU/mL.[79] Limited data from studies that examined primary vaccination strategies in adolescents with HIV and revaccination strategies in adults with HIV suggest modified HepB vaccine dosing regimens—including a doubling of the standard antigen dose and use of combined HepA/HepB vaccine or using the HepB-CpG (Heplisav-b) vaccine—may increase response rates in nonresponders without HIV,[84] adult nonresponders with HIV, and adults and adolescents with HIV undergoing the primary vaccine series.[66,85-89] Therefore, although off-label use of double-dose HepB vaccine or combination HepA/HepB vaccine may be considered for HepB vaccination or HepB-CpG in adolescents (aged ≥14 years) with HIV who are nonresponders, further studies are needed in children.[90] In the ART era, HIV virologic suppression and high CD4 counts have been associated

with higher vaccine responses in children with HIV[77,79,80] during revaccination strategies in those who did not respond to the primary HepB vaccine series.

VII. Should individuals with HIV who have responded to HepB vaccination have ongoing assessment of HBV immunity?

In individuals who have a response to HepB vaccination (anti-HBs ≥10 mIU/mL), assessment of anti-HBs titers approximately every 5 years can be considered.[91,92] If anti-HBs titers fall below 10 mIU/mL, they should be provided a booster. Anti-HBs titers should be checked 4 to 6 weeks after a booster dose **(weak, very low).** If anti-HBs is still <10 mIU/mL, completion of the standard three-dose series should be done.[93]

Waning of anti-HBs levels below 10 mIU/mL after HBV immunization in children with HIV is common.[80] Unlike immunocompetent individuals who have robust B and T cell immune memory, immunocompromised individuals may not mount an anamnestic response. Of individuals with HIV and the isolated HBcAb serologic profile, only 24% to 46% of patients developed an anamnestic response, as defined as an anti-HBs titer ≥10 mIU/mL 4 weeks after one vaccine.[94,95] However, the need for booster doses of HepB vaccine in individuals with HIV has not been determined.[80] 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 if they have an ongoing risk for HBV exposure.[96] One study of nonresponders demonstrated that 92% of children had anti-HBs titers of ≥10 mIU/mL after completion of the vaccine series; the population consisted of either those with primary vaccine nonresponse or waned anti-HBs titers who did not respond to a booster.[97] One study in 10 children with HIV who responded to HepB vaccine found that B-cell memory decreased after 4 years and were below appropriate levels by 6 years post-vaccine.[98] Thus, assessment of anti-HBs approximately every 5 years can be considered in children.

Treatment Recommendations

Treatment Issues in Children and Adolescents With HIV/HBV Coinfection

General Issues: There are excellent reviews of treatment of HBV infection in children.[99] The main difference in children and adolescents with HIV/HBV coinfection is that they will almost always be receiving anti-HIV treatment. This treatment generally will include an agent or agents that have antiviral activity against HBV in addition to antiviral activity against HIV. Understanding the various phases of HBV infection (see the Phases of Chronic HBV Infection table above) is important when considering choices of anti-HIV treatment and in decisions about directed anti-HBV treatment in children and adolescents with HIV/HBV coinfection. Specific directed HBV therapy in children and adolescents with HIV/HBV coinfection is restricted to those individuals in the chronic immunoactive state (HBsAg+, HBeAg+, elevated alanine aminotransferase [ALT], and HBV DNA >20,000 IU for ≥6 months) or with HBeAg-negative chronic hepatitis (HBsAg+, HBeAg-, elevated ALT, and HBV DNA >10,000 IU for ≥6 months). The goals of therapy are generally to normalize ALT, reduce HBV DNA, and in HBeAg-positive individuals, clear HBeAg.[9]

VIII. What ART regimens should be considered for ARV-naive children with HIV/HBV coinfection who are immunotolerant to HBV?

As most children and adolescents with HIV/HBV coinfection will be in the immunotolerant phase, the major issue is what ART regimen is appropriate for HIV/HBV coinfection for those in the immunotolerant phase.

Given the differences in medications currently available for HIV treatment and the desire to include medications with anti-HBV activity, when possible, the Panel recommends the following to minimize the development of resistance in the HBV virus:

- For children aged <2 years, a standard preferred ART regimen should be initiated. While there is a risk for development of 3TC-resistant HBV, the need to provide optimal HIV therapy outweighs this risk **(strong, high).**
- For children aged ≥2 years to <12 years, a standard preferred ART regimen should be initiated. If feasible (weight ≥14 kg), the ART regimen should include tenofovir (TDF or TAF) plus either 3TC or FTC **(strong, low).**
- For children aged ≥12 years, a standard preferred ART regimen including tenofovir (TDF or TAF) plus either 3TC or FTC should be initiated **(strong, low).**

Children with immunotolerant HBV have high HBV DNA levels but no evidence of liver damage. They respond less favorably to HBV treatment, and treatment in this stage of infection is generally not indicated.[9] For children with HIV/HBV coinfection, this presents a dilemma. ART is recommended for all children with HIV, and medications with anti-HBV activity (e.g., 3TC or FTC) are included in the nucleoside reverse transcriptase inhibitor backbone of all regimens recommended as first-line ART, with coadministration of TDF or TAF in children weighing ≥14 kg.[100] However, treatment of HBV with 3TC or FTC as the only HBV-active agent (primarily in children <14 kg) is likely to lead to 3TC/FTC-resistant HBV,[101-103] which may affect future treatment options.

Inclusion of 3TC in an ART regimen has not shown clear benefit in adults with HBV/HIV,[104] and 3TC resistance mutations have been demonstrated in up to 50% of adults with coinfection and continued HBV viremia within 2 years of 3TC monotherapy, and increased to greater than 90% at 4 years.[102,105,106] In a cohort of Thai adolescents with coinfection, 69% had HBV DNA levels above 10^5 copies/mL despite 3TC therapy, and the 3TC resistance mutation rtM204V/I was found in 75% of the adolescents tested.[101] Similarly, in a cohort of children with HIV/HBV coinfection from the Ivory Coast, 6 of 11 (55%) treated with ART containing 3TC failed to show a response to therapy based on continued high HBV DNA levels and/or persistent HBeAg, suggesting a high likelihood of 3TC resistance developing in these children.[107] Studies in children with HBV mono-infection have demonstrated only modest success with 3TC monotherapy, even in children with active HBV disease. In one study, only 23% of children randomized to HBV treatment with 3TC demonstrated suppression of HBV DNA and loss of HBeAg compared to 13% of those treated with placebo.[108] Of the nonresponders to 3TC monotherapy, 64% developed 3TC mutations after 3 years.[103] Therefore, treatment of children with HBV coinfection in the immunotolerant phase with 3TC or emtricitabine as the only HBV-active agent of the ART regimen will likely result in the development of 3TC-resistant HBV, potentially limiting future treatment options.[109,110]

The risk of including 3TC or FTC as the only HBV-active agent in an ART regimen for children must be weighed against the need for optimal HIV treatment. ART should be initiated in infants with

HIV as soon as possible after HIV diagnosis, which would likely be prior to an HBV diagnosis. Given the limited options for ART in children <2 years of age, a standard preferred ART regimen should be provided. The goal for children with coinfection and immunotolerant HBV who are aged ≥2 years should also be optimal HIV treatment. Therefore, a standard preferred ART regimen should be provided. A regimen including TAF and 3TC or FTC should be considered, particularly for children ≥14 kg, based on extrapolation from evidence in adults with HIV/HBV coinfection[109,111,112] and adolescents with HBV mono-infection,[113] but this suggestion is limited by minimal data evaluating the use of TAF for treatment of HBV infection in children or adolescents with HBV mono-infection or HIV/HBV coinfection.[114-116] An ongoing clinical trial of TAF in children and adolescents with HBV infection (NCT02932150) should further clarify this issue in the future.

If a child with coinfection is receiving HIV-suppressive ART including 3TC or FTC and plasma HBV DNA is detectable, HBV 3TC resistance can be assumed, particularly if they have received 3TC for 2 or more years.[101-103,106]

IX. Should 3TC or FTC be the only HBV therapy in children with HIV/HBV coinfection who require treatment of both infections?

Children with HIV/HBV coinfection who require treatment of both infections should not be treated with 3TC or FTC as the only HBV-active agent in the regimen **(strong, moderate).**

The indications for targeting treatment for HBV infection remain the same in individuals with HIV/HBV coinfection as in HBV mono-infection. Treatment directed specifically at HBV is indicated in those children with immunoactive disease and HBeAg-negative chronic hepatitis (see the Phases of Chronic HBV Infection table above).[3,6,99] For all the reasons given in Question VIII, the high risk of development of resistance[102,103,105,106,110] and the impact of resistance on subsequent treatment options,[109,110] 3TC or FTC should not be used alone in an ARV regimen for children who require treatment for both HIV and HBV infection.

X. What treatment regimens should be considered for children with HIV/HBV coinfection who require treatment of both infections?

- For children aged ≥2 years who require treatment for both infections, a combination ARV regimen that includes TDF (or TAF) and an anti-HBV nucleoside (either 3TC or FTC) should be considered for treatment **(strong, low).**
- For children aged ≥2 years, if TDF (or TAF) is not available or not tolerated, entecavir can be added to a standard ARV regimen for HBV treatment **(weak, low).**

If both HBV and HIV treatment are indicated, an ART regimen containing both tenofovir (TAF or TDF) and 3TC or FTC should be considered for use in children aged ≥2 years, based on extrapolation from the evidence in adults[111,112,117,118] and adolescents[116,119] with coinfection and in children[114,115] and adolescents[113,120] with HBV mono-infection. Improved virologic outcomes have been demonstrated in adults with HIV/HBV coinfection treated with tenofovir with and without 3TC or FTC with 77% to 96% achieving suppressed HBV DNA.[111,117,121] Treatment with tenofovir resulted in HBV DNA suppression after 72 weeks of therapy in 89% of adolescents with HBV monoinfection[113] and after 48 weeks in 61% of adolescents with HIV/HBV coinfection,[116] despite prior 3TC exposure. Results of a recently completed clinical trial of TDF in children 2 to 12 years of age with HBV infection (NCT01651403) are available on clinicaltrials.gov.[115] In this study, children (mean 6 years of age) with chronic active HBV were randomized to TDF (n = 60) versus placebo

(n = 30). At Week 48, the percentage of participants treated with tenofovir with a serum HBV DNA level of <400 copies/mL was 83.6% (95% CI, 71.2–92.2) versus 7.7% (95% CI, 0.9–25.1) in those randomized to placebo ($P < 0.001$). More children in the TDF-treated group had ≥4% decrease from baseline in spine bone mineral density at Week 48 compared to those in the placebo group (18.3% vs. 6.9%).

HBV DNA, HBeAg, and liver function should be monitored for response, as in one large study, previous 3TC therapy did affect virologic response to tenofovir in adults with HIV/HBV coinfection.[109]

If tenofovir is not available or not tolerated, addition of entecavir to a fully suppressive ART regimen could be considered. Entecavir has been shown to be effective in children with HBV mono-infection, with HBV suppression achieved in 64% of 120 children treated with entecavir at 96 weeks.[120] However, entecavir should not be used in children with 3TC-resistant HBV, as it only has partial activity, and its use can result in development of entecavir resistance.[110]

While there are limited data on the use of TAF for treatment of HBV in young children (≤ 6 years of age),[122] no evidence suggests TAF should be less effective than TDF. Additional options for treatment of chronic HBV in children are discussed in the American Association for the Study of Liver Diseases Chronic Hepatitis B guidelines.

Agents that also have HIV activity (3TC, FTC, tenofovir, entecavir) should not be used alone without additional antiretroviral agents due to the risk of developing HIV resistance. These agents should only be used in children with HBV/HIV coinfection as a part of or in addition to a fully suppressive ART regimen. See the Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations — Hepatic Events table in the Pediatric Antiretroviral Guidelines. The dose of 3TC required to treat pediatric HIV is higher than that used to treat pediatric chronic HBV infection; therefore, the higher dose of 3TC should be used in children with HIV/HBV coinfection to avoid development of 3TC-resistant HIV. If there is a need to alter the ART regimen due to HIV resistance, care must be taken to not discontinue effective anti-HBV treatment, even if it is ineffective for HIV, as a hepatitis flare may ensue. In other words, the alternative regimen must continue to have effective anti-HBV therapy in the regimen.

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.[3,6,99] Treatment of chronic HBV infection is evolving; consultation with providers with expertise in treating chronic HBV infection in children is recommended.

Children and adolescents with HIV/HBV coinfection are at risk for long-term complications due to the coexistent HBV infection. Monitoring of HBV status and for complications should be part of ongoing care for these individuals.

XI. How often should children with HIV/HBV coinfection be monitored for HBV status and disease activity?

Children with HIV/HBV coinfection who are not receiving HBV-directed treatment should have disease monitoring (ALT for inflammation, complete blood count for platelet count and leukopenia, HBeAg/anti-HBe serostatus, HBV DNA and HBsAg/anti-HBs serostatus) like children with HBV

mono-infection **(strong, moderate).** The value of intermittent noninvasive assessment of hepatic fibrosis with techniques such as transient elastography is unclear.

Proposed Monitoring Based on Phases of Chronic HBV Infection

Status	ALT and CBC	HBeAg/Anti-HBe	HBV DNA	HBsAg/Anti-HBs
Immunotolerant	1–2 times per year	Annually	N/A	N/A
Immunoactive	Every 2 months ×3[a]	Every 6 months	Every 6 months	N/A
Chronic Carrier	1–2 times per year	N/A	N/A	Every 2–3 years
HBeAg-Negative Chronic Hepatitis	Every 2 months ×3[a]	N/A	Every 6 months	N/A

[a] If abnormal ALT persists for 6 months, HBV treatment should be considered.[9]

Key: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; CBC = complete blood count; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus

HBV disease activity should be closely monitored in children with HIV/HBV coinfection, with determination of serum ALT every 6 to 12 months depending on disease status. 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 or escalation of anti-HBV therapy. Assessment of serum transaminases and HBV DNA levels over time can identify individuals 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.[5,6]

Clinical and laboratory exacerbations of hepatitis and hepatic flare also can occur in children with HIV/HBV coinfection receiving ART if agents with anti-HBV activity are discontinued. Generally, once ARV drugs with anti-HBV activity are begun in children with HIV/HBV coinfection, they should be continued indefinitely unless contraindicated. If discontinuation of therapy for chronic HBV infection results in hepatic flare, therapy for chronic HBV should be reinstituted.

The other major risk of chronic HBV infection is the development of HCC. There are conflicting data on whether the risk of HCC is elevated in individuals coinfected with HIV/HBV. As anti-HIV regimens have improved, the risk of HCC does not seem to be increased in individuals coinfected with HIV/HBV above the risk to individuals with chronic HBV infection. However, chronic HBV infection is associated with a lifetime incidence of HCC of 10% to 25%.[123]

XII. How should children with HIV/HBV coinfection be monitored for HCC?

There is no difference in screening for HCC in children with HIV/HBV coinfection compared to children with HBV mono-infection. Surveillance of chronic HBV infection using abdominal ultrasound every 6 months should be performed to detect early HCC in people who have increased (e.g., people with cirrhosis or family history of HCC). Children with a lower risk for HCC should be screened every 1 to 2 years with alpha-fetoprotein (AFP) and every 1 to 2 years with liver ultrasound, or sooner if AFP is >10 mcg/mL **(weak, low).**

There is an increased risk of HCC in individuals with chronic HBV infection.[124] The risk is highest in those who have been infected for more than 40 years and have chronic hepatitis and those with cirrhosis and a family history of HCC.[124] There are no evidence-based guidelines for HCC screening in individuals with HIV/HBV coinfection.[125] There are data showing that adherence to current screening guidelines for individuals with HIV/HBV coinfection is poor.[126] Gelu-Simeon et al. have suggested that specific strategies should be determined for the group with HIV/HBV coinfection,[127] but there are no specific guidelines to date.

There has been only one study of HCC screening that included a significant number of children and adolescents with HBV.[128] That study suggested that screening with twice-yearly AFP with further evaluation, including ultrasound for AFP >15 ng/mL, improved outcomes.[128] They did not use ultrasound screening, as this study predated evidence supporting ultrasound as a preferred tool for HCC screening. A subsequent follow-up study from the same group using ultrasound and AFP >10 ng/mL demonstrated improved detection with combination screening but a higher cost.[129] HCC is also linked to presence of cirrhosis[130] and HBV genotype with genotypes C, D, and F associated with a lifetime higher risk of HCC.[36,124] Thus, some authors have suggested genotype should also influence who is screened for HCC.

XIII. How should children with HIV who are anti-HBc positive be monitored for reactivation of HBV?

Children with HIV who are anti-HBc positive are at risk for HBV reactivation with worsening immunodeficiency or if they are treated with agents associated with a risk of HBV reactivation (e.g., cancer chemotherapy, biologics such as anti-tumor necrosis factor-alpha and direct-acting HCV antiviral therapy). For children initiating rituximab or other B-cell–depleting agents who are not on HBV-active ART, HBV antiviral therapy should be initiated. For children experiencing worsening HIV-related immunodeficiency or who are receiving cancer chemotherapy or high-dose steroids, periodic ALT and HBV DNA monitoring should be considered. For children receiving HCV therapy with direct-acting antiviral (DAA) therapy, children who are HBsAg positive should receive prophylactic HBV treatment as part of their HIV ART, and their HBV DNA should be assessed in the event of hepatotoxicity **(weak, very low).**

Individuals who are HBsAg negative and anti-HBc positive have a risk of latent HBV infection or reactivation of HBV in the setting of increased immunosuppression or with treatment of coexistent HCV with DAAs.[131] Recent guidelines suggest evaluating HBV DNA among individuals who are HBsAg negative and anti-HBc positive, and that administration of a single dose of HepB vaccine should be considered.[9] For those with undetectable HBV DNA, monitoring with ALT and HBV DNA in the setting of increased immunosuppression or treatment of coexistent HCV with DAAs is recommended.[2] An exception is made for those individuals receiving rituximab or B-cell–depleting agents where prophylactic treatment with HBV antiviral therapy is recommended in adults.[9] Those with detectable HBV DNA should be managed as if they have active HBV infection. Consideration should be given to HBV prophylaxis in those at high risk for HBV reactivation.[9]

Dosing Recommendations for Prevention and Treatment of HBV in Children With HIV/HBV Coinfection

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	All Children • HepB vaccine Infants Born to Women With HBV • HepB vaccine plus HBIG	HBIG following exposure	See Figure 1 for detailed vaccine recommendations. Primary Prophylaxis Indicated for— • All individuals who are not infected with HBV Criteria for Discontinuing Primary Prophylaxis • N/A Criteria for Restarting Primary Prophylaxis • N/A
Secondary Prophylaxis	HepA vaccine	N/A	Secondary Prophylaxis Indicated for— • Individuals with chronic HBV infection to prevent further liver injury Criteria for Discontinuing Secondary Prophylaxis • N/A Criteria for Restarting Secondary Prophylaxis • N/A
Treatment	Treatment of Both HIV and HBV Required *Child Not Already Receiving 3TC or FTC* • 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive ART regimen • For children aged ≥2 years, TAF as part of ART regimen with 3TC or FTC • For children aged ≥14 kg to <25 kg, FTC 120 mg/TAF 15 mg FDC once daily • For children ≥25 kg, FTC 200 mg/TAF 25 mg FDC once daily, or 3TC 300 mg plus 25 mg TAF daily	Alternative for 3TC: FTC 6 mg/kg body weight (maximum 200 mg) once daily	Indications for Treatment Include— • Detectable serum HBV DNA, irrespective of HBeAg status, for >6 months; *and* • Persistent (≥6 months) elevation of serum transaminases (≥ twice the upper limit of normal); *or* • Evidence of chronic hepatitis on liver biopsy Choice of HBV treatment options for children with HIV/HBV infection depends upon whether concurrent HIV treatment is warranted. 3TC and FTC have similar activity (and have cross-resistance) and should not

Dosing Recommendations for Prevention and Treatment of HBV in Children with HIV/HBV Coinfection

Indication	First Choice	Alternative	Comments/Special Issues
	• Note: For children weighing <35 kg, FTC/TAF combination should not be used with protease inhibitors for HIV therapy. *Child Already Receiving ART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance* • For children aged ≥2 years, include TDF or TAF as part of ART regimen with 3TC or FTC. o For children aged <12 years, TDF 8 mg/kg body weight per dose once daily (maximum dose 300mg) o For children aged ≥12 years, TAF 25 mg once daily • For children aged ≥12 years, add entecavir 0.5 mg by mouth once daily in addition to ART regimen.		be given together. FTC is not FDA-approved for treatment of HBV. TAF is approved for use in treatment of HIV 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 children with HIV/HBV coinfection as part of an ART regimen. Entecavir is approved for use in children without HIV ≥2 years of age for treatment of chronic HBV. It should only be used for HBV in children with HIV/HBV coinfection who also receive an HIV-suppressive ART regimen but cannot use or access tenofovir. IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6–12 weeks of ART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS. In children receiving TDF or TAF 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 >12 months after HBeAg seroconversion and can be closely monitored on discontinuation. If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening.

Key: 3TC = lamivudine; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; FDA = U.S. Food and Drug Administration; FDC = fixed dose combination; FTC = emtricitabine; HBeAg = hepatitis B antigen; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HepA = hepatitis A [vaccine]; HepB = hepatitis B [vaccine]; IRIS = immune reconstitution inflammatory syndrome; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Hepatitis C Virus Infection

Updated: January 28, 2026
Reviewed: January 28, 2026

Panel's Recommendations

I. Do children with HIV/hepatitis C virus (HCV) coinfection warrant any specific surveillance or monitoring beyond what is recommended for HIV mono-infection and HCV mono-infection?

Children with HIV/HCV coinfection should receive the same routine care and monitoring that is recommended for children with HIV mono-infection and children with HCV mono-infection (strong, moderate).

II. Should infants born to women known to have hepatitis C be tested for HCV infection, and if yes, when and how?

Testing for HCV infection should be performed on any infant or child whose mother is known to have hepatitis C (strong, high).

As per Centers for Disease Control and Prevention guidelines, all pregnant women should be tested for hepatitis C with each pregnancy.

All children perinatally exposed to HCV should receive a nucleic acid test (NAT) for HCV RNA at age 2–6 months. If not performed earlier, NAT for HCV RNA can be performed at age 7–17 months (strong, high).

A negative NAT for HCV RNA at age 2–6 months is highly suggestive (>99% negative predictive value) of no perinatal transmission. For those not tested earlier, negative anti-HCV immunoglobulin G testing at 18 months is confirmatory of no HCV (strong, low).

In consultation with a health care provider with expertise in pediatric hepatitis C management, children who test positive for HCV RNA should have follow-up care through age 3 years to assess eligibility for HCV treatment (strong, high).

III. For infants and children born to women with HIV/HCV coinfection, do specific obstetric or infant feeding practices reduce the risk of perinatal transmission of HCV?

Recommendations on route of delivery and intrapartum management are the same for HIV/HCV coinfection and HIV mono-infection. Unlike HIV, available data suggest breastfeeding does not pose an appreciable risk of transmission to infants of mothers with HCV. Risk of HCV transmission via breastfeeding in the setting of HIV/HCV coinfection is likely similar to HCV mono-infection, although no data currently exist. Decisions regarding appropriate feeding practices in infants born to mothers with HIV/HCV coinfection should be determined on a case-by-case basis guided by shared decision making and driven by maternal HIV virological status. Mothers should abstain from breastfeeding from nipples that are cracked or bleeding or breasts affected by mastitis (strong, moderate).

IV. For women with HIV/HCV coinfection, does treatment of HCV infection with sustained virologic response prior to pregnancy (as opposed to no treatment or treatment failure) reduce the risk of HCV perinatal transmission?

Women with HIV/HCV coinfection who are of childbearing potential and wish to become pregnant should be evaluated for treatment of HCV infection prior to conception. They should be treated for HCV infection to reduce their risk of liver disease progression and perinatal transmission of HCV (strong, high).

Ribavirin-containing regimens are no longer recommended for treatment of HCV infection given the availability of safer and more efficacious treatment options (strong, high).

There are no large-scale clinical trials evaluating the safety of pangenotypic direct-acting antiviral (DAA) regimens during pregnancy. Treatment can be considered on an individual basis after a discussion of the potential risks and benefits (strong, low).

See details in the HCV/HIV Coinfection section of the Perinatal Guidelines and the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance for pregnancy.

V. What counseling should an adolescent with HIV receive to reduce the risk of HCV acquisition/transmission?

All adults and adolescents with HIV should be counseled to avoid injection drug use. If using drugs, they should—

- Avoid reusing and/or sharing needles, *and*
- Be tested for HCV and hepatitis B virus, *and*
- Receive appropriate referral and therapy for substance use disorder (**strong**, **high**).

Unprotected sex has been linked to HCV transmission, so all adolescents—including those with HIV, multiple sex partners, or sexually transmitted infections—should be advised to use barrier protection (**strong**, **moderate**).

VI. Among children with HIV/HCV coinfection, which vaccinations to reduce risk of liver disease are available?

Hepatitis A and hepatitis B vaccines are recommended for all children, including those with hepatitis C with or without HIV coinfection, with follow-up serologic confirmation of vaccine response (**strong**, **low**).

VII. For all children with HCV mono-infection or HIV/HCV coinfection, what are the indications for HCV treatment?

Any child aged 3 years or older with HCV mono-infection or HIV/HCV coinfection should receive treatment with a pangenotypic DAA regimen (**strong**, **moderate**).

VIII. For all children with hepatitis C, what U.S. Food and Drug Administration (FDA)–approved medications are available for those requiring treatment?

Either of the FDA-approved pangenotypic DAA regimens (sofosbuvir/velpatasvir or glecaprevir/pibrentasvir) can be used for treatment (**strong**, **high**).

For more information about evaluation for DAA treatment, visit the AASLD/IDSA HCV in Children webpage.

IX. When treating children with HIV/HCV coinfection, are there significant drug–drug interactions between HCV and HIV treatment regimens that require consideration?

Clinically relevant drug–drug interactions have been identified between current FDA-approved pediatric DAA regimens and multiple classes of antiretroviral drugs that may warrant alternate therapy, dose adjustment, or extra monitoring. Reference to current AASLD/IDSA HCV guidance on patients with HIV/HCV coinfection is recommended (**strong**, **high**).

Rating of Evidence

Strength of Recommendation: Strong; Weak

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

Epidemiology

The prevalence of hepatitis C virus (HCV) infection among children in the U.S. National Health and Nutrition Examination Survey was 0.2% (aged 1–11 years) to 0.4% (aged 12–19 years) in the 1990s[1,2] and fell to less than 0.1% in the subsequent decade.[3] A recent modeling study estimated a prevalence of 0.03% for children aged 0 to 11 years and 0.05% for children aged 12 to 18 years.[4] Centers for Disease Control and Prevention (CDC) modeling predicts that approximately 1,700 new cases of perinatally acquired pediatric HCV infection occur annually.[5] The prevalence of HCV infection among children with HIV may be significantly higher, with HCV coinfection documented among 1.5% of 535 children with HIV in U.S. pediatric HIV clinical trials in 2003.[6] Higher rates of HCV infection have been documented in some international cohorts of children with HIV, likely due

to increased risk of HCV perinatal transmission in pregnant women with poorly controlled HIV infection.[7,8]

Perinatal transmission is the predominant mode of HCV acquisition in infants and younger children.[9,10] Injection drug use is the predominant route of infection in older children; less common modes of transmission include noncommercial body piercing or tattooing, unintentional needle stick injury, household contact or sharing of potentially contaminated personal items, and sexual exposure.[11,12] Before 1992, blood transfusion was a key route of HCV transmission in the United States.

The overall risk for perinatal HCV transmission from a woman with HCV mono-infection ranges from 4% to 10%.[9,13-21] 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] HCV genotype does not appear to affect the 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 overall perinatal HCV transmission.[10,15,16,18,29-33] In addition, even though HCV RNA can be detected in breast milk, studies of infants born to women with HCV have not demonstrated a higher risk of HCV transmission in breastfed infants than in those who are formula fed.[10,13-16,18,25,28,29,34]

Early studies demonstrated that maternal HIV/HCV coinfection increased the risk of perinatal transmission of HCV, with perinatal HCV transmission rates of 6% to 23% reported for infants born to women with HIV/HCV coinfection.[9,13-15,19,26,30-32,35-40] Furthermore, a few studies suggested that children who have HIV during the perinatal period may be more likely than those who do not have HIV to acquire HCV from mothers with HIV/HCV coinfection.[30,31,37,38] Dual virus transmission was reported in 4% to 10% of children born to mothers with HIV/HCV coinfection.[13,30,35,37,39] HCV RNA levels are hypothesized to be higher among women with HIV/HCV coinfection than in those with HCV mono-infection, which could account, in part, for the increased risk of perinatal HCV transmission from pregnant women with HIV/HCV coinfection. However, not all studies have found higher levels of HCV viremia in mothers with HIV/HCV coinfection.[24,31,36] Several recent studies in the era of routine combination antiretroviral therapy (ART) during pregnancy found that the risk of perinatal HCV transmission is far lower than rates found in historical studies when few or no antiretrovirals (ARVs) were available, suggesting that perinatal transmission of HCV may be significantly reduced in women with HIV who are receiving ART.[40,41]

Recommendations on route of delivery, intrapartum management, and infant feeding are the same for HIV/HCV coinfection and HIV mono-infection. Further details are available in the Perinatal Guidelines and Pediatric Antiretroviral Guidelines.

The incidence of HCV infection in adolescents and young adults has been increasing since 2010. Data from the CDC show an increase in the incidence of acute HCV infection among people aged 20 to 29 years from 0.75 cases per 100,000 population in 2010 to 2.2 cases per 100,000 population in 2022. The incidence rate of acute HCV infection in people aged 20 to 29 years peaked in 2018 at 3.0 cases per 100,000 population, which was the highest at the time but now surpassed by the rate in 30 to 39 year olds of 3.6 cases per 100,000 in 2022.[42] The incidence of HCV infection is higher in rural areas, and the majority of new infections are in people with a history of injection drug use (IDU).[43-47] HIV is a significant risk factor for HCV acquisition in men who have sex with men (MSM).[46,48] MSM with HIV who were followed in the Multicenter AIDS Cohort Study (MACS)

from 1984 to 2011 were almost six times more likely to acquire HCV than MSM who did not have HIV (incident risk ratio 5.98). The incidence rate for HCV infection in MSM with HIV recruited to MACS between 2005 and 2011 was 5.16 per 1,000 person-years.[49] The incidence of HCV infection was somewhat lower in a cohort of MSM with HIV in Boston tested between 2008 and 2009 who had an annualized incidence of 1.63 per 1,000 person-years. Risk factors for HCV acquisition included noninjection drug use and a history of sexually transmitted infections.[50]

Clinical Manifestations

The clinical course of HCV infection appears to be more benign in children with perinatal hepatitis C than in adults with newly acquired hepatitis C.[11,51,52] Most children with hepatitis C are asymptomatic; however, some may experience nonspecific symptoms—such as fatigue, myalgias, and poor weight gain—and develop hepatomegaly.[11,52,53] Intermittent asymptomatic elevations in transaminase levels are common during the first 2 years of life.[53-56] Across studies of children with hepatitis C, 20% to 65% 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.[57,58]

Histopathologic inflammatory changes of chronic hepatitis may be present in children with chronic hepatitis C despite a lack of symptoms, normal serum transaminases, and low HCV RNA levels.[53] 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% of specimens, and cirrhosis in 2% of specimens.[59] Most children with chronic hepatitis C 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.[11,24,52,55] Similar proportions of children with perinatally and parenterally acquired HCV 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 or transfusion-acquired hepatitis C for a mean duration of 13 years, 12% had significant fibrosis on liver biopsy.[52] Older age at time of infection and elevated serum gamma-glutamyl transpeptidase correlated with fibrosis; serum transaminase levels correlated with inflammation.[52]

In adults with HIV/HCV coinfection, the natural history of HCV infection appears to be accelerated, with more rapid progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death.[60,61] Reports on the effect of ART and immune reconstitution on liver-related mortality in adults with HIV/HCV coinfection are conflicting; some studies show decreases, but others show little difference in liver-related mortality.[62,63] 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 children with HIV/HCV coinfection.[9] In a study from Spain in the early ART era comparing children with perinatal HIV/HCV coinfection to those with perinatal HCV mono-infection, HCV viremia and maximum transaminase levels were higher in the children with HIV/HCV coinfection than in those with HCV mono-infection.[64]

Data on the impact of HCV on HIV disease progression in adults are conflicting. Some studies suggest that HCV accelerates HIV progression, but others show no such effect.[9] The effect of pediatric HIV/HCV coinfection on HIV disease progression is also unclear because the number of children with HIV/HCV coinfection is small and only a few studies have evaluated any potential association. Two studies of children with perinatal HIV/HCV coinfection found no increase in HIV progression. In a study of older children with thalassemia who had HIV or HIV/HCV coinfection

through transfusion, disease progression was more rapid and mortality was higher in those with HIV/HCV coinfection than in those with HIV mono-infection.[30,39,65]

Diagnostic Assays

Both serologic assays for anti-HCV antibodies and nucleic acid tests (NATs) for HCV RNA are used to diagnose HCV infection. HCV RNA first becomes detectable 1 to 2 weeks after HCV acquisition, preceding the rather delayed antibody seroconversion that occurs an average of 7 to 8 weeks after acquisition.[66] Third-generation enzyme, chemiluminescent, and microparticle immunoassays for anti-HCV immunoglobulin G have high sensitivities and specificities, though sensitivities are lower in patients with HIV with severe immunosuppression and in acute infection prior to seroconversion. A U.S. Food and Drug Administration (FDA)–approved rapid saliva test is also available for screening adolescents and adults aged 15 years and older.[67,68]

A reactive HCV antibody test can represent current infection or past cleared infection, and the presence of HCV RNA, or HCV viremia, is indicative of current HCV infection. Diagnosis of hepatitis C requires a NAT for HCV RNA, and highly sensitive quantitative real-time polymerase chain reaction (PCR) or transcription-mediated amplification NATs have lower limits of detection of 10 to 15 IU/mL and broad quantitative range.[69]

Treatment

The goal of HCV treatment is to achieve sustained viral response (SVR12; absence of viremia 12 weeks after therapy is complete), which has been shown in adults to reduce the risk of progressive liver fibrosis and hepatocellular carcinoma. Secondary benefits of successful therapy include prevention of transmission of HCV and relief from HCV-related stigma. Because liver disease progresses slowly in most children, no rationale exists currently for urgent treatment of most cases of pediatric HCV. Many children previously included in HCV treatment studies had little or no fibrosis.[70] The relatively few children with more significant fibrosis and/or cirrhosis were often treated.[71]

The current standard of care for adults with hepatitis C is a combination of several direct-acting antivirals (DAAs) that target different HCV proteins. The DAAs are administered orally once a day, leading to rapid and consistent viral clearance, and have a very favorable side effect profile. Two pangenotypic DAA regimens are FDA approved for use in children with hepatitis C who are ages 3 years and older: sofosbuvir/velpatasvir and glecaprevir/pibrentasvir.[72-74] Each of these regimens has weight-based dosing and child-friendly formulations that make administration relatively simple.

Management Recommendations

Do children with HIV/HCV coinfection warrant any specific surveillance or monitoring beyond what is recommended for HIV mono-infection and HCV mono-infection?

Children with HIV/HCV coinfection should receive the same routine care and monitoring that is recommended for children with HIV mono-infection and children with HCV mono-infection ***(strong, moderate).***

Due to conflicting data about the rate of disease progression in children with HIV/HCV coinfection compared to that among children with either HIV mono-infection or HCV mono-infection, no

specific additional measures need to be implemented. Surveillance and diagnostic measures recommended for children with HIV/HCV coinfection include those recommended for children with HIV mono-infection and those recommended for children with HCV mono-infection. The involvement of a specialist with experience treating HCV is suggested.

Diagnosis and Testing Recommendations

Making the Diagnosis

Should infants born to pregnant women known to have hepatitis C be tested for HCV, and if yes, when and how?

Testing for HCV should be performed on any child whose mother is known to have hepatitis C ***(strong, high).***

As per CDC guidelines, all pregnant women should be tested for hepatitis C with each pregnancy.

All children perinatally exposed to HCV should receive a NAT for HCV RNA at age 2 to 6 months. Infants and children aged 7 to 17 months who have not previously been tested should receive a NAT for HCV RNA. Children aged ≥18 months who previously have not been tested should receive an anti-HCV test with reflex to NAT for HCV RNA when anti-HCV is reactive ***(strong, high).***

Undetectable HCV RNA at age 2 to 6 months is highly suggestive (>99% negative predictive value) of perinatal transmission. Perinatally exposed children aged ≥18 months with nonreactive anti-HCV test results do not have hepatitis C ***(strong, low).***

Infants and children with detectable HCV RNA should be managed in consultation with a provider with expertise in pediatric hepatitis C management and receive regular follow-up care until eligible for HCV treatment at age 3 years ***(strong, high).***

Passively transferred maternal HCV antibody can be detected up to age 18 months in infants born to women with hepatitis C. In a large cohort of children who were HCV exposed but uninfected, anti-HCV antibody was present in 15% of children at 12 months, 5% at 15 months, and 2% at 18 months.[24] Infants who are perinatally exposed to HCV should, therefore, not be tested for anti-HCV before age 18 months. Only the detection of HCV viremia can be used to diagnose HCV infection in at-risk infants aged <18 months.[75]

HCV infection can be diagnosed in infants with perinatal exposure by a NAT to detect HCV RNA after age 1 month. The sensitivity of the HCV RNA testing was low (22%) at birth but increased to 79% at age 1 month and 85% at 6 months in a multisite European study published in 2006.[76] A more recent single-site study utilizing high-sensitivity HCV RNA reverse transcription PCR assays to diagnose perinatal HCV infection at age 2 to 6 months reported a sensitivity of 100% (95% confidence interval, 87.5% to 100%).[77] The use of early NAT at 2 to 6 months is recommended by the CDC to identify infants with hepatitis C, given concerns about loss to follow-up before HCV antibody testing can be done at age ≥18 months.[76]

When testing children age ≥18 months an HCV antibody test when reactive should always be followed automatically by a NAT for HCV RNA. HCV antibody testing without reflex to HCV RNA when antibody is reactive, is incomplete testing. The detection of HCV RNA confirms current HCV infection, and detected HCV RNA should be managed in consultation with a provider with expertise

in pediatric hepatitis C management until eligible for HCV treatment at age 3 years. Children aged 3 years or older should receive HCV treatment.

Prevention Recommendations

Primary Prevention

Preventing Exposure

For infants and children born to women with HIV/HCV coinfection, do specific obstetric or infant feeding practices reduce the risk of HCV perinatal transmission?

Recommendations on route of delivery and intrapartum management are the same for HIV/HCV coinfection and HIV mono-infection. No strategy to prevent perinatal HCV transmission has been studied. Elective cesarean delivery is not associated with reduced perinatal transmission of HCV and is not recommended for this purpose for pregnant women with current hepatitis C. Maternal HIV/HCV coinfection does not alter the current recommendation for scheduled cesarean delivery for people with HIV who have HIV RNA levels >1,000 copies/mL near delivery to prevent perinatal HIV transmission.

Observational studies inconsistently associate prolonged duration of ruptured amniotic membranes, internal fetal monitoring, and perineal lacerations/episiotomy with increased risk of HCV transmission.[24,41,78]

Available data suggest breastfeeding does not pose an appreciable risk of transmission to infants born to mothers with HCV.[79] Risk of HCV transmission via breastfeeding in the setting of HIV/HCV coinfection is likely similar to that of HCV mono-infection, although no data currently exist. Decisions regarding appropriate feeding practices in infants born to mothers with HIV/HCV coinfection should be determined on a case-by-case basis guided by shared decision making and driven by maternal HIV virological status. Mothers should abstain from breastfeeding from nipples that are cracked or bleeding or breasts affected by mastitis. **(strong, moderate).**

In the setting of HIV/HCV maternal coinfection, testing the infant's HCV RNA PCR one additional time within 6 months after cessation of breastfeeding can be considered, regardless of the age of the infant at the time of breastfeeding cessation. Risks of HCV transmission and HIV transmission via breastfeeding in the setting of HIV/HCV coinfection are likely similar to risks in HCV mono-infection and HIV mono-infection, respectively, although no data currently exist. Infant feeding recommendations for people with HIV/HCV do not differ from recommendations for people with HIV who do not have HCV. For guidance about infant feeding for people with HIV,[80] see the Preventing HIV Transmission During Infant Feeding section of the Perinatal Guidelines.

For women with HIV/HCV coinfection, does treatment of HCV with sustained virologic response prior to pregnancy (as opposed to no treatment or treatment failure) reduce the risk of HCV perinatal transmission?

Women with HIV/HCV coinfection who are of childbearing potential and wish to become pregnant should be evaluated for treatment of HCV ***prior*** *to conception. They should be treated for HCV to reduce their risk of liver disease progression and the risk of perinatal transmission of HCV* ***(strong, high).***

Ribavirin-containing regimens are no longer recommended for treatment of HCV given the availability of safer and more efficacious treatment options ***(strong, high).***

There are no large-scale clinical trials evaluating the safety of pangenotypic DAA regimens in pregnancy. Treatment can be considered on an individual basis after discussion of the potential risks and benefits ***(strong, low).*** *For more information, see the HCV/HIV Coinfection section of the Perinatal Guidelines and the AASLD/IDSA guidance for HCV in pregnancy.*

No clinical trials have specifically assessed the efficacy of the treatment of maternal HCV to prevent future perinatal transmission. However, in observational studies in pregnant women who are anti-HCV reactive, those who lack detectable viremia do not transmit HCV to their children, with only rare exceptions that may relate to low-level or fluctuating maternal viremia. Thus, therapy to eradicate HCV viremia prior to pregnancy is expected to eliminate the risk of perinatal transmission. This option was not previously readily feasible because of the safety concerns for interferon and ribavirin in pregnancy, particularly the teratogenic side effects of ribavirin that preclude its use starting 6 months prior to conception and its potential transfer to infants by a breastfeeding mother.[81] The availability of highly effective interferon- and ribavirin-free combinations of all-oral DAA therapies for HCV infection that are safe in animal models of pregnancy offer a safe option for treating people prior to conception to both cure the infection and prevent future perinatal transmission of HCV.

A small study evaluating the pharmacokinetics of ledipasvir/sofosbuvir in pregnancy demonstrated 100% SVR12 and no safety concerns. Similarly, an international case series of 15 pregnant women treated with ledipasvir/sofosbuvir reported 100% SVR12 and no early safety concerns in the women or their infants.[82,83] Currently, data on the use of pangenotypic regimens during pregnancy are limited, with clinical trials in progress.[84] However, treatment can be considered on an individual basis after a patient–physician discussion about potential risks and benefits.

What counseling should an adolescent with HIV receive to reduce the risk of HCV transmission?

All adults and adolescents with HIV should be counseled to avoid injection drug use. If using drugs, they should—

- Avoid reusing and/or sharing needles,
- Be tested for HCV infection and hepatitis B virus (HBV) infection at a frequency aligned with their ongoing exposure, *and*
- Receive appropriate referral and therapy for substance use disorder **(strong, high).**

Unprotected sex has been linked to HCV transmission, so adolescents with HIV and those with multiple sex partners or sexually transmitted infections should be advised to use barrier protection ***(strong, moderate).***

Other potential exposures to HCV, such as tattooing and body piercing, should also be avoided ***(weak, low).***

No HCV preventative or prophylactic vaccine is available. IDU is the most reported risk factor for HCV infection in the United States. Increased IDU among rural and urban adolescents and young adults has fueled increases of new infections among individuals aged <40 in the United States since

2006, with the highest rates in nonurban communities. This change in epidemiology prompted the current recommendation for one-time screening of all adults 18 years and older and for pregnant women during each pregnancy.[85] Although adolescents were not included in the recommendation, adolescents are among those with IDU and often have been diagnosed with hepatitis C when they are admitted to the hospital after an overdose.[86] Given these circumstances, it is appropriate to adapt HCV screening and testing to younger populations or more frequent intervals based on ongoing risk of HCV exposure.

Multiple outbreaks of HCV infection have been reported among MSM with HIV who do not use injection drugs, linked most strongly with inconsistent condom use and other high-risk practices, including having sex while intoxicated on drugs and having multiple sexual partners. In the era of the message "Undetectable = Untransmittable" or U=U, education about the need to continue to use barrier protection to protect against sexual acquisition of HCV, regardless of HIV status, is important.

Preventing the First Episode of Disease

For children with HIV/HCV coinfection, which vaccinations to reduce risk of liver disease are available?

Hepatitis A and hepatitis B vaccines are recommended for all children, including those with hepatitis C with or without HIV coinfection, with follow-up serologic confirmation of vaccine response ***(strong, low).***

Patients with chronic liver disease, HIV, or both can develop fulminant hepatitis from hepatitis A virus (HAV) or HBV infection.[87] Patients with advanced HCV-related liver disease, HIV, or both may not mount an appropriate immune response to vaccines.[88] Therefore, measurement of HAV and HBV antibody titers 1 to 2 months after completion of the vaccination series is recommended. For more information, see the Hepatitis B Virus section of the Pediatric Opportunistic Infections Guidelines.

Treatment Recommendations

For all children with hepatitis C and children with HIV/HCV coinfection, what are the indications for HCV treatment?

All children aged ≥3 years should receive treatment with an approved pangenotypic DAA regimen regardless of disease severity ***(strong, moderate).***

With prior interferon-based HCV treatment or early versions of DAA regimens, concerns about cost, side effects, and complicated administration prevented these agents from being used for widespread treatment. Currently available pangenotypic DAA regimens can cure virtually all patients with HCV mono-infection and HIV/HCV coinfection; therefore, treatment should be offered to all eligible patients regardless of whether they were previously treated. Evaluation for DAA treatment has been simplified with fewer laboratory tests required prior to initiation.

For more information about evaluation for and monitoring on DAA treatment, visit the AASLD/IDSA HIV guidance on HCV in children.

For all children with hepatitis C, what FDA-approved medications are available for those requiring treatment?

Either of the FDA-approved pangenotypic DAA regimens (sofosbuvir/velpatasvir or glecaprevir/pibrentasvir) can be used for treatment ***(strong, high).***

Two pangenotypic DAA regimens are now approved for use in children as young as 3 years old: sofosbuvir/velpatasvir and glecaprevir/pibrentasvir. Both agents offer similar efficacy in curing HCV infection, and preference for one versus the other should be based on whichever agent is most easily obtained from public or private insurers for the individual patient.

For more information about dosing by age and weight, visit the AASLD/IDSA HIV guidance on HCV in children.

When treating children with HIV/HCV coinfection, are there significant drug–drug interactions between HCV and HIV treatment regimens that require consideration?

Clinically relevant drug–drug interactions have been identified between current FDA-approved pediatric DAA regimens and multiple classes of ARV drugs that may warrant alternate therapy, dose adjustment, or extra monitoring. Referral to current AASLD/IDSA HCV guidance is recommended ***(strong, high).***

Because treatment of HIV/HCV coinfection includes the challenge of dosing separate multidrug regimens, many studies have examined potential drug interactions. The Patients With HIV/HCV Coinfection section of the AASLD/IDSA HCV Guidance offers a detailed discussion of these potential interactions and should be consulted when considering treatment of any kind. This section includes a summary table to quickly screen for potential drug interactions between HCV DAAs and HIV ARVs. In addition, a summary table on the same webpage offers a quick resource for screening for potential drug interactions.

A few key considerations include the following:

- Velpatasvir can increase concentrations of tenofovir disoproxil fumarate and lead to tenofovir-related renal toxicity. It is unclear at this time whether this is also the case with tenofovir alafenamide. Nevertheless, care should be taken in those patients with reduced creatinine clearance.[89]
- Concentrations of velpatasvir, glecaprevir, and pibrentasvir are significantly reduced when co-administered with efavirenz.[90,91] Thus, both currently approved pediatric pangenotypic DAA regimens (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) are to be avoided in children taking non-nucleoside reverse transcriptase inhibitors, including efavirenz, etravirine, or nevirapine. No interactions are expected with rilpivirine with either pangenotypic regimen.
- Glecaprevir co-administration is contraindicated with atazanavir and not recommended with ritonavir-boosted ART regimens due to elevated glecepravir concentrations.

Dosing Recommendations and Important Considerations for HCV Antiviral Therapy in Children and Adolescents With HIV

- The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C virus (HCV) management. See the AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C for more details.
- For detailed dosing recommendations for HCV antiviral therapy in children and adolescents, refer to the section on HCV in Children.
- For more information on other important considerations in the management of HCV in children and adolescents with HIV—such as drug–drug interactions, alternate therapies, dose adjustment, and extra monitoring—refer to the section on Patients With HIV/HCV Coinfection.

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Herpes Simplex Virus

Updated: June 27, 2018
Reviewed: June 27, 2018

Panel's Recommendations
I. Will condoms (compared with not using condoms) prevent herpes simplex virus (HSV) infection in sexually active adolescents and young adults with HIV? • Condoms should be used to prevent HSV infection (and other sexually transmitted diseases) in adolescents and young adults with HIV (strong; low). The data regarding the level of protection provided by condoms are very limited for individuals with HIV in general, and for youth specifically.
II. Will adolescents and young adults with HIV who have recurrent, genital HSV infection benefit from suppressive anti-HSV antiviral therapy (compared with not using suppressive therapy)? • Adolescents and young adults with HIV who suffer severe, frequent, and/or troubling recurrent genital HSV infection will benefit from anti-HSV suppression therapy (strong; moderate).
III. Should children and adolescents with HIV who have severe primary or recurrent HSV (genital or orolabial) infection receive intravenous (IV) acyclovir (compared with receiving oral antiviral therapy)? • Children and youth with HIV who have severe mucocutaneous HSV infections should be treated with IV acyclovir. When improvement is noted, they can be switched to oral therapy until healing is complete (strong; moderate).
IV. Should children and adolescents with HIV be treated with oral acyclovir, valacyclovir, or famciclovir for non-severe primary episodes or recurrent episodes of orolabial or genital HSV (compared with no antiviral therapy)? • Oral anti-HSV drugs will shorten the duration and reduce the severity of non-severe HSV infections in children and adolescents with HIV. Oral valacyclovir and famciclovir have superior pharmacokinetic profiles compared with oral acyclovir (strong; moderate).
V. Is foscarnet the best choice for anti-HSV therapy for children and adolescents with HIV in whom therapy is failing because of acyclovir-resistant HSV? • Foscarnet is the therapy of choice for acyclovir-resistant HSV (strong, very low). Ideally, the viral isolate should be tested to determine the antiviral resistance pattern.
Rating System *Strength of Recommendation: Strong; Weak* *Quality of Evidence: High; Moderate; Low; or Very Low*

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 sex 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

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	None	None	Primary prophylaxis is not indicated.
Secondary Prophylaxis	Mucocutaneous Disease • Acyclovir 20 mg/kg body weight/ dose (maximum 800 mg/dose) by mouth BID Suppressive Therapy After Neonatal HSV Disease (Skin, Eye, Mouth, CNS, or Disseminated Disease) • 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 • Valacyclovir 500 mg by mouth BID, *or* • Famciclovir 500 mg by mouth BID	Secondary Prophylaxis Indicated • Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease. Criteria for Discontinuing Secondary Prophylaxis • 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	Neonatal CNS or Disseminated Disease • Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for ≥21 days Neonatal Skin, Eye, or Mouth Disease • Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for 14 days CNS or Disseminated Disease in Children Outside the Neonatal Period • 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	• 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. • Recurrent genital HSV can be treated with valacyclovir 500 mg BID for 3 days or 1 g by mouth daily for 5 days. • Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth BID for 1 day. • 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.	For Neonatal CNS Disease • 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. • 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.

	Moderate to Severe Symptomatic Gingivostomatitis • 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. Mild Symptomatic Gingivostomatitis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 7–10 days Recurrent Herpes Labialis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 5 days For First-Episode Genital Herpes (Adults and Adolescents): • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 7–10 days Recurrent Genital Herpes (Adults and Adolescents) • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 5 days Children with HSV Keratoconjunctivitis • 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. Children with ARN • For children old enough to receive adult dose, acyclovir	• Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth BID at a 12-hour interval for 2 doses. • 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. Acyclovir-Resistant HSV Infection • 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).	• Famciclovir is available in a sprinkle formulation with weight-adjusted dosing. Famciclovir can be used by adolescents able to receive adult dosing. Alternative and Short-Course Therapy in Immunocompromised Adults with Recurrent Genital Herpes • Acyclovir 800 mg per dose by mouth BID for 5 days • Acyclovir 800 mg per dose by mouth TID for 2 days 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.

	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 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. **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.** 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. Criteria for Discontinuing Primary Prophylaxis: • N/A Criteria for Restarting Primary Prophylaxis: • 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: • Documented histoplasmosis in a patient with impaired immune function Criteria For Discontinuing Secondary Prophylaxis *If All of the Following Criteria Are Fulfilled:* • CD4 percentage >15% at any age; or CD4 cell count >150 cells/mm^3 aged ≥6 years. • Received ≥1 year itraconazole maintenance therapy • Established (e.g., ≥6 months) adherence to effective cART • Negative *Histoplasma* blood cultures • Serum Histoplasma antigen <2 ng/mL 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: • 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. Mild Disseminated Disease: • 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: • Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily Mild Disseminated Disease: • 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. 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. 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 <u>Moderately Severe to Severe Disseminated Disease</u> *Acute Therapy (Minimum 2-Week Induction, Longer if Clinical Improvement is Delayed, Followed by Consolidation Therapy):* • Liposomal amphotericin B 3–5 mg/kg body weight, IV once daily (preferred) • Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) *Consolidation Therapy (Followed by Chronic Suppressive Therapy):* • 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 <u>Central Nervous System Infection</u> *Acute Therapy (4–6 Weeks, Followed by Consolidation Therapy):* • Liposomal amphotericin B, 5 mg/kg body weight IV once daily **(All)** *Consolidation Therapy (Followed by Chronic Suppressive Therapy):* • 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 <u>Moderately Severe to Severe Disseminated Disease</u>: • 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. • Liposomal amphotericin B 3–5 mg/kg body weight IV once daily (preferred) for 4–6 weeks • 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. High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered. Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy. 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 Disease

Updated: December 22, 2025
Reviewed: December 22, 2025

Panel's Recommendations
• Human papillomavirus (HPV) vaccination is recommended in people with HIV aged 9–12 (AIII) and for those aged 13–26 years who have not been previously vaccinated or have not completed the vaccine series (AIII). • Ideally, HPV vaccine should be administered before an individual becomes sexually active (AIII). • HPV vaccination is recommended starting at the age of 9 years for children with a history of sexual abuse. • Bivalent, quadrivalent, and nonavalent HPV vaccines are approved in the United States, but only the nonavalent vaccine is currently available in the United States. Three doses are recommended for all people with HIV, regardless of sex or age at which the vaccine was administered. • If the bivalent or quadrivalent vaccine was previously administered, revaccinating with a three-dose series using the nonavalent vaccine should be considered (CIII). • Regardless of vaccination status, screening for cervical cancer should start at age 21 years (see the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines) (AIII). • Latex condoms should be used during every act of vaginal, anal, and oral sexual intercourse to reduce the risk of exposure to sexually transmitted pathogens, including HPV (AII). • Anogenital warts in children should be treated per the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infections Treatment Guidelines.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence: I = One or more randomized trials **in children**† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials **in adults** with clinical outcomes and/or validated laboratory endpoints with accompanying data **in children**† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies **in children**† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies **in adults** with long-term clinical outcomes with accompanying data **in children**† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *†Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents*

Epidemiology

This chapter focuses primarily on prepubescent and pubescent children with HIV. Prepubescent is before puberty, generally age 0 to 8 years. Pubescent means attained puberty but not fully mature, which varies individually, but is generally started by age 13 in most females and by age 14 in most males in the United States. For complete recommendations on older adolescents (postpubescent defined by reaching sexual maturity rating 4), refer to the Human Papillomavirus Disease section of the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV.

Human papillomavirus (HPV) infects cutaneous and mucosal squamous epithelium. More than 200 distinct types of HPV exist.[1] The majority of HPVs of clinical importance fall predominantly into the alpha HPV genus.[1] HPV can be detected on normal healthy mucosal and cutaneous surfaces but also is associated with anogenital warts in children and anogenital and oropharyngeal precancers

and cancers in adults and, in rare cases, in adolescents. HIV reflects a significant increased risk of HPV-associated disease in adults including cervical, anal, vulvar, and vaginal precancers and cancers and oropharyngeal cancers.[2] All of these precancers and cancers are rare in the general population.[3] In contrast, people who were previously treated for a childhood cancer have a fourfold to eightfold increase in oropharyngeal cancers and a ninefold to 14-fold increase for anal cancers, with the youngest age at diagnosis being 10 years of age.[4] How this translates to children with HIV is uncertain. The HIV status of the rare cases of cervical and anal cancers in children is unknown. Both cutaneous and anogenital warts also reflect a significant burden in children and adults with HIV.[5]

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 HPV (hr-HPV) types. Of the approximately 40-plus genital (i.e., mucosal) HPV types, 12 types have been established as hr-HPV (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.[6] Of the HPV-associated vulvar, vaginal, penile, and oropharyngeal cancers, 50% to 80% also are attributed to HPV16.[7-9] Skin warts associated with HPV are common in children, whereas mucosal warts (including anogenital and oral warts) are less common.[10-14]

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, 10, 27, and 57 and are associated with distinct wart histology.[15,16] The estimated prevalence of skin warts in immunocompetent children varies widely by population. A British cohort study of 9,263 schoolchildren found 3.9% prevalence at age 11 years and 4.9% prevalence at age 16 years, while a Dutch study of 1,465 schoolchildren found 15% prevalence at age 4 years that rose to 44% at age 11 years.[11,12,17] 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 rates of skin warts in children with HIV. One retrospective study in South Africa examined 65 children presenting for treatment of anogenital warts. Out of the 23 children who required surgical intervention, those who were known to have HIV (12 patients) required a significantly higher number of surgical procedures to reach clinical resolution, compared to those known to not have HIV (6 patients).[18]

HPV-associated anogenital warts are known to be transmitted by sexual contact, thereby raising the concern of sexual abuse when diagnosed in prepubertal children.[14,19] 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[20] or through other nonsexual means (e.g., autoinoculation or transmission from the hands or mouth of a caretaker).[21-23] 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 prepubertal children,[13] 0.17% of children referred to a tertiary care hospital,[14] and 1.8% in children with suspected sexual abuse.[24] HPV6 and HPV11 are the most common types detected in anogenital warts in children,[25] though cutaneous HPV types have also been detected.[26] A multicenter study in Germany found mucosal HPV types were more common in anogenital wart biopsies from those under 5 years of age, whereas cutaneous HPV types were more common in anogenital wart biopsies from those 5 to 12 years old.[27] In one study of children with anogenital warts, 24% of children had an adult family member with anogenital warts, 62% had a mother with cervical intraepithelial neoplasia (CIN), and 48% had a family member with extragenital warts,[28] suggesting that nonsexual transmission is a possible route of infection. Studies of self-inoculation are lacking in children, but

one adult study of 25 monogamous couples reported evidence of self-inoculation in 11 males and 4 females.[29] In a systematic review, among children with anogenital warts, older age was associated with a higher odds for sexual abuse (odds ratios [ORs] were 6.5–7.5 for children aged 3–4 years, 5–8 years, and 9–12 years, compared with 0–2 years).[30] Also, genital location (i.e., penile or vulvar) was associated with a higher odds (OR 5.93) for sexual abuse compared to the perianal location.

Oral papillomas also have been described in children, as well as sexually active adolescents, and are commonly associated with HPV6 and HPV11. A rarer condition that is also associated with HPV6 and HPV11 is juvenile onset recurrent respiratory papillomatosis (JORRP), which can be life threatening due to the risk of airway obstruction from wart lesions in the respiratory tract.[31,32] JORRP is a chronic condition that is more aggressive compared to adult onset recurrent respiratory papillomatosis (or AORRP), and management is limited to repeated surgical resection and few adjuvant treatment options. As this condition is not reportable, disease epidemiology is challenging to study. Data in the United States published in 1995 estimated an incidence of 4.3 per 100,000 children, compared to 1.8 per 100,000 adults.[33] A more recent systematic review published in 2024 estimated an incidence in the pre-vaccine era that ranges from 0.2 to 2.1 per 100,000 children, and a prevalence rate that ranges from 0.8 to 4.3 per 100,000.[34] Recent studies show a decline in JORRP with increasing HPV vaccine coverage, exemplified by an incidence rate ratio (IRR) of 0.2 between births in 2012 through 2013 compared with births in 2004 through 2005.[35] No data are available on its epidemiology in children with HIV.

Detection of HPV DNA in normal tissue of infants has been documented, suggesting that perinatal transmission also can occur.[36] Rates of HPV DNA detected in newborns vary significantly (0% to 70%), and when found in the infant, HPV type concordance between the mother and infant also is quite variable (<1% to 100%).[37-39] A systematic quantitative review of maternal–neonatal transmission concluded that pooled perinatal HPV transmission was around 6.5%.[37] Several authors have suggested that the rate of HPV detection in infants depends on the rate found in pregnant mothers.[38,40] Risks of DNA detection in newborns include maternal HPV status at delivery and the presence of anogenital lesions (i.e., condyloma or squamous intraepithelial lesions) in the mother.[38,39] Studies have concluded that pregnancy itself, even in the setting of HIV infection, is not associated with increased vulnerability to HPV acquisition.[41] In addition, women with cervical cancer are not likely to transmit HPV to their children.[42] However, women with HIV, in general, are much more likely to have HPV infections.

In one study, 19.7% of infants born to mothers with HPV and 16.9% of infants born to mothers who were HPV negative at delivery were found to be HPV positive in their mouth or anogenital area at some time during a mean follow-up period of 14 months, suggesting that perinatal transmission is not the sole source of oral or genital HPV infection in infants.[38] Although maternal history of condyloma at time of delivery has been a well-described risk factor for appearance of JORRP, the risk remains quite low, with estimates of 7 per 1,000 births with a maternal history of genital warts.[43] In a parent–child study in Finland, the cumulative detection rates for high-risk HPV from the child's genital and oral samples were 36% and 42%, respectively.[44] However, persistence of HPV was less common, with persistent oral HPV in 10% of infants and persistent genital HPV in 1.5% of infants. A relatively recent systematic review of the prevalence of HPV in pediatric tonsils showed a range from 0% to 21%; the largest study observed no infections.[45] Together, these data show that in the general population oral and genital perinatal transmission can occur, whereas persistence is unusual when infection is acquired (whether through vertical or horizontal transmission).

Even less is known about HPV detection in normal tissue in children with HIV. A study of adolescents with perinatally acquired HIV showed that 30% of girls had an abnormal (atypical SCs of undetermined significance [ASC-US] or greater) Pap test.[46] The mean age at the time of the first Pap test 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, maternal HIV was noted to be a risk factor for neonatal transmission.[40] Another study of adolescents with perinatal HIV aged 11 to 16 years in Côte D'Ivoire found an HPV prevalence of 3.6% for all HPV types and a prevalence of 2.8% for oncogenic HPV obtained from vaginal swabs collected by a midwife.[47] Of the 250 participants, 12 (4.8%) reported having had vaginal intercourse. Interestingly, risk for HPV was not associated with vaginal intercourse, whereas the practice of intravaginal cleansing with water only or water plus soap was significantly associated with HPV infection even when accounting for vaginal intercourse. In a small study of 50 girls aged ≤18 years who reported never having sexual contact, 30% of the girls who acquired HIV perinatally had HPV detected from external genital samples compared to 7% of girls who were perinatally exposed but uninfected.[48] HPV DNA also was found to be twice as common in the oral cavity than in the HIV-uninfected control group.[49] Of interest, 21% of women with HIV were found to have HPV, including hr-HPV and low-risk HPV types, detected in breast milk samples.[50] These data together suggest that children with perinatally acquired HIV may be more vulnerable to maternal transmission of HPV because of higher rates of HPV in this group of mothers and higher rates of HPV persistence in the neonatal and infant period due to immunosuppression. Unfortunately, there are no large mother–infant studies of HPV transmission and persistence in women with HIV.

Genital HPV is most commonly a result of sexual transmission. Epidemiology of genital HPV is covered in Adult and Adolescent Opportunistic Infection Guidelines.[2] Rates of HPV are higher in adolescents and adult women with HIV than those without HIV.[51-53] As with HPV, CIN and condyloma also are more common in women with HIV.[54-58]

Although the incidence of anogenital HPV infection in sexually active youth is high, longitudinal studies have demonstrated that 80% to 90% of infections in youth without HIV are transient and spontaneously regress.[59-61] Although anal HPV acquisition is associated with anal intercourse, several studies in both children and adults suggest that other sexual and nonsexual routes of anal acquisition are possible.[60,62,63]

The higher prevalence of HPV infections in populations with HIV may result partly from increased HPV persistence in these patients. In one study of adolescents with HIV, approximately 50% cleared their HPV infections.[57] Detection of anal HPV also is higher in youth with HIV.[62]

Persistent infection with hr-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 women and men. Rates of HPV-associated cancers—including cervical, vulvar, vaginal, penile, anal (men and women), and oropharyngeal—are higher in individuals with HIV[64-66] and believed to result predominantly from the increased risk of persistent infection in this group. For adolescents, refer to the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines.

Although combination antiretroviral therapy (ART) 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 ART,[67-69] whereas cervical cancer rates have decreased in most racial and ethnic groups. In contrast, anal cancer rates have increased in

individuals with HIV.[70] The increase in cervical precancer and decrease in cervical cancer is thought to be due to increased cervical cancer screening, leading to earlier detection and treatment of precancers and therefore lower rate of cancers.

Other risks associated with of cervical cancer include lack of cervical cancer screening, prolonged use of hormonal contraception, parity, smoking, and immunocompromising conditions other than HIV.[71]

Clinical Manifestations

Genital, Anal, Skin, Oral, and Respiratory Tract 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 acuminata. Warts can be single or present with multiple lesions and often appear as papules or flat, smooth, or pedunculated lesions. Common sites for skin warts are the hand, elbows, knees, and feet. Another manifestation of warts in the respiratory tract is JORRP, which 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 neoplasia are asymptomatic. Cancers associated with hr-HPV types include cervical, vulvar, vaginal, penile, anal, and oropharyngeal, specifically at the base of the tongue and tonsils. Cancers often are 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.[10] In some instances, anogenital warts can raise suspicion for sexual abuse. If sexual abuse is suspected, referring to clinics specializing in providing abuse evaluations should be considered.[10] Speculum examination is not recommended for prepubertal children in the office setting. If intravaginal lesions from HPV or sexual abuse are suspected, appropriate referral to an expert in pediatric gynecology and in sexual abuse is recommended as vaginoscopy maybe required and should be performed under anesthesia. Anoscopy or a digital rectal examination is not routinely indicated. 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

Cytology is not recommended in non–sexually active prepubescent children with HIV nor in those who have been sexually abused. However, if intraepithelial or SC cancers are suspected, the same cytology and colposcopic techniques used to detect CIN in people without HIV should be used in

people with HIV. Cytology is a screening test for cervical cancer (see the Prevention section below). 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, anal, and oral cancers often can be palpated by digital examination of the vaginal, vulvar, intra-anal, and oral pharyngeal regions. Definitive diagnoses are made by histology. CIN, AIN, VAIN, and VIN can often be visualized using colposcopy and high-resolution anoscopy, but definitive diagnosis is made by biopsy.

Role of Human Papillomavirus DNA/RNA Testing

HPV testing is not helpful in diagnosing or managing visible genital, skin, or oral warts. HPV testing is not recommended in any circumstance for adolescent girls or boys (aged <20 years), regardless of whether they have HIV, because of the high rates of HPV infection.[2] High rates of HPV infection do not implicate disease necessarily as most HPV infections will spontaneously regress, even among those with HIV. HPV testing is currently not recommended in the case of sexual abuse.

Prevention Recommendations

Preventing Exposure

If sexually active, individuals with HIV should use latex or polyurethane condoms during every act of vaginal, anal, and oral sexual intercourse to reduce the risk of exposure to (or transmission of) sexually transmitted pathogens **(AII).** Efficacy of condoms is covered in the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines.

Human Papillomavirus Vaccine

The bivalent, quadrivalent, and nonavalent vaccines have been shown to prevent HPV16 and HPV18 infections and associated precancers in females. The quadrivalent vaccine has been shown to prevent HPV16 and HPV18 infections and precancers in males, and immunobridging studies for the nonavalent vaccine suggest equal protection. The quadrivalent and nonavalent vaccines also protect against HPV6 and HPV11 infections and associated genital warts in females and males; the nonavalent vaccine also protects against five other oncogenic HPV types (31, 33, 45, 52, 58).[72-75] After 2016, only the nonavalent vaccine has been available in the United States. Because the HPV vaccine prevents infection and is not therapeutic, it ideally should be administered before potential exposure to HPV through sexual contact **(AIII).** Studies of HPV vaccine in adults with HIV have shown little to no therapeutic efficacy.[73,76,77] There are no randomized clinical trials in those with HIV in the age group 13 to 26 years of age.

The nonavalent HPV vaccine is recommended for routine vaccination of females and males with HIV aged 9 to 12 years **(AIII)** and for those aged 13 to 26 who have not been previously vaccinated or have not completed the vaccine series **(AIII)** (see the Use of 9-Valent Human Papillomavirus [HPV] Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices). A three-dose series is recommended regardless of the age when the vaccination was started. 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.

If the vaccination schedule is interrupted, the series can be continued and does not need to be restarted. The nonavalent HPV vaccine may be used to complete a series started with the

quadrivalent or bivalent vaccines. Currently, for those with HIV, three doses are recommended at any age, which is in contrast to the general population, for whom two doses are recommended for those younger than age 15 years.[10] A three-dose series of the HPV vaccine is recommended starting at the age of 9 years[78] in those with a history of sexual abuse. For those who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give an additional full series (three doses) of vaccination with recombinant nonavalent vaccine, but no data exist to define who might benefit or how cost effective this approach might be **(CIII).** The additional five hr-HPV types covered by the nonavalent vaccine were found in 4.2% to 18.3% of HPV-associated cancers in men and women in the United States, depending on the cancer's location.[79] If the person had severe immunosuppression at the time of initial HPV vaccination, re-immunizing with the HPV vaccine should be considered once immune reconstitution is achieved.

Human Papillomavirus Vaccine Efficacy

HPV vaccine studies in immunocompetent children and adults show excellent immunogenicity, efficacy, and safety.[10] Based on clinical trials and immunobridging studies, the Advisory Committee on Immunization Practices recommends routine vaccination for 11 to 12 year olds with a statement that the HPV vaccination series can be administered starting at 9 years of age.[80] The American Academy of Pediatrics now recommends starting the vaccine series anytime between ages 9 and 12, in consideration of the best timing for family acceptance and completion of the vaccine series.[10] This was based on retrospective observational data that showed that initiation of the vaccine at ages 9 to 10 years was associated with greater on-time completion of the series (by age 15), compared to initiation at ages 11 to 12.[81,82] Although recent evidence suggests that one dose of the HPV vaccine has reasonable protection in healthy people, a single dose is not currently endorsed in the United States at any age[83,84] and is not recommended for those with HIV.[85] HPV vaccine studies in adults with HIV show lower but measurable antibodies[86] compared to adults without HIV. Unfortunately, little data on efficacy were collected in these studies. Few studies of HPV vaccine in children with HIV are available.[87]

To date, studies of children with HIV show similar findings as studies of adults with HIV with lower but measurable antibodies compared with individuals without HIV. In the only randomized clinical trial of the quadrivalent HPV vaccine for children with HIV in the United States, researchers found the vaccine to be safe and immunogenic in children aged 8 to 11 years.[88] Serum antibodies to HPV6 and HPV18 were 30% to 50% lower than in historic age-matched immunocompetent controls. Eighteen months after the third vaccine dose, 94% to 99% had antibodies to HPV6, HPV11, and HPV16; however, only 76% had antibodies to HPV18. This group also was given a fourth dose, which demonstrated an excellent amnestic response for all the vaccine-associated HPV types.[89] After a follow-up period of 2.5 to 4 years, antibody titers were higher in the four-dose group, although seropositivity rates were similar to those who had received three doses.[90] Lower antibody titers were correlated with lower CD4 T lymphocyte (CD4) percentage and with higher CD8 percentage and HIV RNA. Most other non-randomized vaccination studies show similar or slightly lower seroconversion rates in children with HIV compared with children without HIV, with decreasing seropositivity over time, particularly for anti-HPV18 titers; in one study, only 67% were positive at 24 months postvaccination.[87,91,92] One trial of children with HIV aged 9 to 14 years old in Kenya with three quadrivalent HPV doses found high seroconversion rates 12 months postvaccination; 4 years postvaccination, seropositivity rates were 77% for HPV18, 80% for HPV11, 83% for HPV6, and 90% for HPV16.[87,91] Antibody titers remained higher for those with undetectable versus detectable HIV RNA at time of vaccination. One study has examined a two-dose schedule in children aged 9 to 15 years with good immune reconstitution. The comparison group consisted of youth aged 15 and

older with or without immune reconstitution and children aged 9 to 15 without immune reconstitution who received a three-dose schedule. In this study, girls received the bivalent vaccine whereas boys received the quadrivalent vaccine. The geometric mean titers (GMTs) for HPV16 and 18 were similar 1 to 3 months after the last dose between the two groups for both boys and girls; longer-term data were not available.[93]

In a randomized trial comparing the bivalent and quadrivalent vaccines in 546 young women aged 15 to 25 years (257 with HIV and 289 without HIV), GMT was higher for those without HIV versus those with HIV. Antibody titers peaked at 1 month and plateaued by Month 24. Antibody response was higher for those with perinatally acquired HIV than for those with sexually transmitted HIV.[94]

Few studies have examined efficacy. In a single-arm, open-label study, incident rates of persistent HPV in 279 girls and women with HIV vaccinated with the quadrivalent HPV vaccine were compared to previously published rates for vaccinated women without HIV.[95] In the per protocol efficacy population, after a mean follow-up of 2 years, the rate ratio for persistent HPV for women with HIV versus women without HIV using reported rates was 11.7 (95% confidence interval [CI], 2.6–52.1), demonstrating reduced efficacy in women with HIV. This study had several limitations, including its relevance to children given that most participants were adults.

There has been interest in single-dose HPV vaccination; in 2022, the World Health Organization recommended single-dose vaccination as an option for girls and boys aged 9 to 20 years. This recommendation was not extended to individuals known to be immunocompromised or people with HIV.[85] In an observational study in the United States and Puerto Rico, HPV vaccine–type antibody levels were measured from stored sera in 310 youth with perinatally acquired HIV and 148 youth who were perinatally HIV exposed but without infection. GMTs were lower for all HPV vaccine types in those with perinatally acquired HIV. However, GMTs were similar whether participants received one, two, or three doses. For all four types, younger age, lower HIV viral load at first vaccine dose, and fewer years from last vaccine dose to sample collection were each independently associated with higher GMTs. The cumulative prevalence of abnormal cervical cytology (ASC-US or greater) was almost 60% for girls with perinatally acquired HIV and 4% for those who were perinatally exposed to but did not acquire HIV.[96] Among girls who were sexually active and vaccinated with the quadrivalent HPV vaccine, the IRR for those with perinatally acquired HIV was 5.2 (95% CI, 0.7–41.7) compared with youth who have exposure to but who do not have HIV. When restricted to those who initiated vaccination prior to sexual debut, the IRR was attenuated but those with perinatally acquired HIV continued to be at higher risk (IRR = 3.0; 95% CI, 0.4–25.7). The number of vaccine doses, GMTs, and number of sexual partners were not associated with abnormal cytology. There were marginal associations with low CD4, high viral load, and lack of ART at first vaccination dose. Most recently, a South African study evaluated single-dose bivalent HPV vaccination.[97] This study conducted repeat cross-sectional surveys among adolescent girls aged 17 to 18 years. The vaccine program was available to girls from one school district aged 15 to 16 years old in 2019. The postvaccine survey included those who had been eligible for that vaccine program. The prevaccination survey recruited girls from the same school district aged 17 to 18 years old in 2019 and therefore too old for the vaccination program. HPV16 and HPV18 prevalence was lower in the postvaccination survey versus the prevaccination survey (adjusted prevalence ratio = 0.65; 95% CI, 0.51–0.83), with no difference by HIV status. Ongoing studies will continue to evaluate the efficacy and duration of immune response in youth with HIV.

Preventing Disease

Circumcision

There is evidence that circumcision in males without HIV reduces the rates of oncogenic HPV infection of the penis[98-103] and is associated with lower risk of penile cancer[104,105] and cervical cancer in sexual partners.[106] The prevalence of hr-HPV has a relatively wide variability, ranging from 0% to 83%.[107,108] Because of the lack of studies in those with HIV and the lack of benefit suggested by other studies,[109] evidence is insufficient to recommend infant or adult male circumcision solely for the purpose of reducing the risk of oncogenic HPV infection in those with HIV or their sex partners in the United States.

Preventing Cervical Cancer

Women with HIV should have cervical screening cytology (liquid-based or Pap test) when they have reached the age of 21 years, regardless of their sexual history, as per the Adult and Adolescent Opportunistic Infection Guidelines **(AIII).** Cytology is not recommended in non–sexually active prepubescent children with HIV nor in those who have been sexually abused.[110]

Preventing Vaginal and Vulvar Cancer

Routine screening for vaginal or vulvar cancer in children with HIV is not recommended.

Preventing Anal Cancer

Anal cancer screening in children with HIV is not recommended.

Treatment Recommendations

Treating Disease

Treating HPV-Associated Warts

Multiple treatment options for HPV-associated skin and external genital lesions are typically offered to adults and adolescents, as no single treatment is universally ideal for all patients or all lesions.[111] It is important to note that no topical treatment is approved by the U.S. Food and Drug Administration for genital warts for those under age 12, because there are few studies of safety and efficacy in children.[112,113] If untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. Regression of cutaneous (nongenital) and genital warts occurs in approximately 30% of cases within 6 months and 90% in several years, even without treatment.[10] Thus, monitoring for spontaneous resolution is a reasonable option. Considerations that may prompt treatment for those under age 12 are similar to considerations for older patients, including symptoms (itching, burning, discomfort). They may also be associated with secondary infections or considerable psychosocial distress about the appearance. However, in children, treatment decisions must consider their sensitive skin, low pain tolerance, and potential for psychological distress regarding treatment itself. For instance, repeated applications of uncomfortable topical treatments may be poorly tolerated for some patients. There are no clinical guidelines available for pain management for children receiving treatment for HPV-associated lesions. Clinicians may attempt using common topical anesthetics used in other routine pediatric procedures such as lidocaine

2.5%/prilocaine cream 5% (sold as EMLA), but evidence for efficacy is lacking. In cases of strong indication for treatment and concern for pain and/or psychological distress, sedation could be considered.

Treatment guidelines for anogenital warts are found in the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infections Treatment Guidelines and apply to both populations with HIV and those without HIV.[111] Treatment can induce wart-free periods, but the underlying viral infection can persist, with potential for recurrence, especially for individuals who are immunosuppressed due to HIV. Immunosuppressed patients may have larger or more numerous warts and may not respond as well as immunocompetent individuals to treatment.[111,114-116] Topical treatments may be ineffective in patients with large or extensive lesions.

As stated in the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines, patient-applied or parent-applied treatments include podofilox (0.5%) solution or gel **(BIII),** imiquimod (3.75% or 5%) cream **(BII),** and sinecatechins (15%) ointment **(BIII).**[112,113,117-119] Topical podofilox 0.5% is approved for use in adults aged >18 years, and some limited small studies in children have found efficacy rates similar to older patients, with minimal side effects.[117,120] Imiquimod 3.75% or 5% is approved for use in children >12 years, and limited case reports support the safety and efficacy in younger children.[117,121-123] Sinecatechins 15% is approved for use in adults aged >18 years and also has limited case reports for children.[118,119] Because some treatments are contraindicated in pregnancy, women who might be pregnant should be advised on how to avoid exposure while applying them to their child.

For warts for which provider-applied topical treatments might be more appropriate, no data are available on the use of bichloroacetic acid (80% to 90% aqueous solution) in children. Trichloroacetic acid (TCA) is an option; however, limited data exist on its use in children **(BIII).**[112,113,124,125] Because TCA is a powerful acid, great care should be taken to avoid applying an excess amount. If an excess amount is inadvertently applied, immediate steps should be taken (e.g., cover with baking soda, wash with liquid soap, or powder with talc) to neutralize the excess acid to avoid further injury or scarring of the surrounding skin.

Alternative treatments for adults include cidofovir topical gel (1%), intralesional interferon-alfa (IFN-α), 5-fluorouracil (5-FU)/epinephrine gel implant, or podophyllin resin. Cidofovir gel (1%) is a topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection. Evaluation of cidofovir for anogenital warts in children is lacking, but a limited number of case reports support the option of cidofovir for recalcitrant cutaneous (nongenital) warts in children **(CIII).**[126-130] The precaution is that topical cidofovir can be absorbed systemically and is known to be nephrotoxic and has been associated with renal failure.[131] Injectable therapy (such as with IFN-α or 5-FU/epinephrine gel implant) has not been evaluated in children and should be offered only by a qualified expert in severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects **(CIII).** Although off-label, intralesional cidofovir with variable formulations has also been used for recalcitrant warts.[132] Podophyllin resin (10% to 25%) should not be used in children, due to risks of neurotoxicity, bone marrow suppression, and liver dysfunction.

Lesions can be removed by cryotherapy or surgery **(BIII).** Cryotherapy (application of liquid nitrogen or cryoprobe) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1 to 2 weeks, up to four times. Lesions can be removed surgically by tangential scissor, tangential shave excision, curettage, or electrosurgery.

Limited data are available on treatment of oral warts in people with HIV. Limited lesions can be treated with provider-applied therapies, such as TCA or surgical excision. Extensive lesions should be referred to an expert.[135]

Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removing all disease.

Treating Histologically Confirmed CIN, VIN, VAIN, AIN, and Anogenital Cancers

For adolescents with HIV who have CIN, VIN, VAIN, AIN, or anogenital cancers, refer to the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines.

Role of Antiretroviral Therapy

Severe immunosuppression is associated with greater HPV-associated morbidity and mortality and lower HPV vaccine immunogenicity and efficacy. Maintaining low viral load and a normal CD4 cell count is recommended. HPV vaccine should be administered at the time of optimal immune health. Depending on the circumstances, it may be best not to defer awaiting immune reconstitution; rather, re-immunize once immune reconstitution is reached.

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 sinecatechins ointment is inflammation at the application site. The major toxicity of cryotherapy is local pain and skin irritation, which can be tolerable for adults but challenging for children and should be discussed with caregivers. Adequate local pain management is essential for all caustic treatments. Topical anesthetics are favored, but use of such anesthetics may not be sufficient, and traditional distraction techniques would be another concurrent approach in children.[133,134] 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. Topical cidofovir can be absorbed systemically and is known to be nephrotoxic and has been associated with renal failure.[131] Intralesional IFN-α can be associated with systemic toxicities of IFN-α, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Scarring can occur with any of the above treatment modalities. Topical cidofovir may result in systemic absorption and can be associated with renal toxicity.[131]

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, postoperative 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 adults with HIV has been observed in which occurrence of oral warts was associated with decreased HIV RNA levels with ART.[136] Immune reconstitution in response to viral load reduction may result in a return of marked inflammatory responses against latent oral HPV infection. Some studies,[136,137] but not others,[138] have reported an increase in oral warts following ART initiation.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines. No recommendations exist for preventing recurrence of external genital warts.

Managing Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy and is more common in those with HIV compared to general population. 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. See the Human Papillomavirus Disease section of the Adult and Adolescent Opportunistic Infection Guidelines for management of recurrence of anogenital intraepithelial lesions.

Discontinuing Secondary Prophylaxis

This consideration is not applicable.

Dosing Recommendations for Prevention and Treatment of Warts Associated With Human Papillomavirus in Children

Indication	First Choice	Alternative*	Comments/Special Issues
Primary Prophylaxis	HPV vaccine	N/A	See Figure 1. Recommended Immunization Schedule for Children With HIV Infection Aged 0 to 18 Years for detailed vaccine recommendations.
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	Monitoring for spontaneous resolution is a reasonable option; 30% resolve spontaneously within 6 months and 90% within several years. Patient- or Parent-Applied Treatment Options • Imiquimod (3.75% or 5%) cream applied topically at night and washed off in the morning for 3 nonconsecutive nights a week for up to 16 weeks (BII). • Podofilox (0.5%) solution/gel applied topically two times daily for 3 consecutive days a week. Withhold treatment for 4 days and repeat the cycle weekly up to four times (BIII). • Sinecatechins (15%) ointment applied three times daily for up to 16 weeks, until warts are cleared completely and not visible (BIII). Provider-Applied Treatment Options • TCA (80% to 90%) applied topically weekly for up to 3 to 6 weeks (BIII).	Patient- or Parent-Applied Treatment Options • Cidofovir topical gel (1%) is an experimental therapy studied in adults with HIV that is commercially available through compounding pharmacies and has very limited use in children; systemic absorption can occur with potential for renal toxicity (CIII). Provider-Applied Treatment Options • Intralesional IFN-α and 5-FU/epinephrine gel implant are generally not recommended because of high cost, difficult administration, potential for systemic side effects, and lack of testing in children (CIII). * These alternative therapies should include consultation with infectious disease and dermatological specialists.	When choosing treatment options, parent and child comfort in application should be considered. Children have a low pain threshold and, generally, sensitive skin. Adequate topical anesthetics to the genital area should be given before caustic modalities are applied. For young children, these approaches are poorly tolerated due treatment-related and postoperative pain, and as a result may require general anesthesia. Therefore, these should be mainly reserved for children with extensive lesions. Many of these agents are contraindicated in pregnancy and have potential teratogenic effect. When treatment options are considered, the potential for pregnancy should be discussed and proper precautions during pregnancy explained.

	• Cryotherapy with liquid nitrogen or cryoprobe applied every 1 to 2 weeks up to four times (BIII). • Surgical removal either by tangential excision, tangential shave excision, curettage, or electrosurgery (BIII).		ART has not been consistently associated with reduced risk of HPV-related abnormalities in individuals with HIV. Most treatments for genital warts cannot be used in the oral mucosa; some oral warts can be treated with TCA or surgical excision. Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removing all disease.

Key: 5-FU = 5-fluorouracil; ART = antiretroviral therapy; HPV = human papillomavirus; IFN-α = interferon-alfa; TCA = trichloroacetic acid

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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: • 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. Second-Line Alternative: • 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. 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. 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 Second-Line Alternatives: • Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth twice daily for 7 days • Nitazoxanide (see doses below) for 3 consecutive days *Children Aged 1 Year–3 Years:* • Nitazoxanide 100 mg by mouth every 12 hours *Children Aged 4 Years–11 Years:* • Nitazoxanide 200 mg by mouth every 12 hours *Adolescents Aged ≥12 Years and Adults:* • 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. The optimal duration of treatment with pyrimethamine has not been established. 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

Updated: November 6, 2013
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 (https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria). 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

https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria). 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 https://phil.cdc.gov/Details.aspx?pid=339). 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. 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 https://www.cdc.gov/malaria/php/case-reporting/index.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 https://www.cdc.gov/immigrant-refugee-health/hcp/domestic-guidance/malaria.html?). 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.

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 https://www.cdc.gov/malaria/hcp/clinical-guidance/malaria-treatment-tables.html.

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 (https://www.ncbi.nlm.nih.gov/books/n/whomalaria/pdf/). An interactive web-based resource for checking on drug interactions involving ARV drugs is found at the University of Liverpool website 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: 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 https://www.cdc.gov/immigrant-refugee-health/hcp/domestic-guidance/malaria.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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Dosing Recommendations for Prevention and Treatment of Malaria

Indication	First Choice	Comments/Special Issues
Primary Prophylaxis	For Travel To Chloroquine-Sensitive Areas: • 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 • Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home o 11–20 kg; 1 pediatric tablet (62.5 mg/25 mg) o 21–30 kg, 2 pediatric tablets (125 mg/50 mg) o 31–40 kg; 3 pediatric tablets (187.5 mg/75 mg) o >40 kg; 1 adult tablet (250 mg/100 mg) • 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 • Mefloquine 5 mg/kg body weight orally given once weekly (max 250 mg) For Areas with Mainly *P. Vivax*: • 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	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/ 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*. G6PD screening must be performed prior to primaquine use. Chloroquine phosphate is the only formulation of chloroquine available in the United States; 10 mg of chloroquine phosphate = 6 mg of chloroquine base.

Indication	First Choice	Comments/Special Issues
	For Travel to Chloroquine-Resistant Areas: • Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home o 11–20 kg; 1 pediatric tablet (62.5 mg/25 mg) o 21–30 kg; 2 pediatric tablets (125 mg/50 mg) o 31–40 kg; 3 pediatric tablets (187.5 mg/75 mg) o >40 kg; 1 adult tablet (250 mg/100 mg) • 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 • Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg)	For travel to chloroquine-resistant areas, preferred drugs are atovaquone/proguanil, doxycycline (for children aged ≥8 years) or mefloquine
Secondary Prophylaxis	For *P. vivax* or *P. ovale*: • 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. http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#1939
Treatment	Uncomplicated *P. Falciparum* or Unknown Malaria Species, from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region: • Atovaquone-proguanil (pediatric tablets 62.5 mg/25 mg; adult tablets 250 mg/100 mg), dosed once daily: o 5–8 kg; 2 pediatric tablets for 3 days; o 9–10 kg; 3 pediatric tablets for 3 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. 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) For most updated prevention and treatment recommendations for specific region, refer to updated CDC treatment table available at

Indication	First Choice	Comments/Special Issues
	o 11–20 kg; 4 pediatric tablets or 1 adult tablet for 3 days; o 21–30 kg; 2 adult tablets for 3 days; o 31–40 kg; 3 adult tablets for 3 days; o >40 kg; 4 adult tablets for 3 days Uncomplicated *P. Falciparum* OR Unknown Malaria Species From Chloroquine-Sensitive Region (See Comments for Link to Resistance Map): • 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) *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (All Areas Except Papua New Guinea, Indonesia; See Comments) *Initial Therapy (Followed by Anti-Relapse Therapy for P. Ovale and P. Vivax)*: • 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) *Anti-Relapse Therapy for P. ovale*, *P. vivax*:	https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_202306.pdf For sensitive and resistant malaria by country: https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/yellow-fever-vaccine-malaria-prevention-by-country 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: • Atovaquone-proguanil plus primaquine phosphate • Quinine sulfate plus EITHER doxycycline OR tetracycline PLUS primaquine phosphate. This regimen cannot be used in children aged <8 years. • Mefloquine plus primaquine phosphate

Indication	First Choice	Comments/Special Issues
	• Primaquine 0.5 mg base/kg body weight (max 30 mg base) by mouth once daily for 14 days Uncomplicated *P. falciparum* or Unknown Malaria Species from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region: • 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 • 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. • 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. o 5 to <15 kg; 1 tablet per dose o 15 to <25 kg; 2 tablets per dose o 25 to <35 kg; 3 tablets per dose o >35 kg; 4 tablets per dose	

Indication	First Choice	Comments/Special Issues
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) PLUS One of the Following: • 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 OR • Clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours for 7 days. OR • 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 Artesunate 2.4 mg/kg body weight IV bolus at 0, 12, 24, and 48 hours PLUS One of the Following: • Doxycycline (treatment dosing as above), or • Atovaquone-proguanil (treatment dosing as above), or • 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 • 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. 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. Quinidine gluconate: 10 mg = 6.25 mg quinidine base. Doxycycline (or tetracycline) should be used in children aged >≥ 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. 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. Drug Interactions: • Avoid co-administration of quinidine with ritonavir • Use quinidine with caution with other protease inhibitors.

Key: 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?
• Effective antiretroviral therapy (ART) is the primary initial treatment for microsporidiosis in HIV-infected children (strong, very low).
• Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (expert opinion).
• Albendazole, in addition to ART, is also recommended for initial therapy of microsporidiosis caused by microsporidia other than *Enterocytozoon bieneusi* and *Vittaforma corneae* (strong, low).
• Systemic fumagillin (where available), in addition to ART, is recommended for microsporidiosis caused by *E. bieneusi* and *V. corneae* (strong, moderate).
• Topical therapy with fumagillin eye drops, in addition to ART, is recommended in HIV-infected children with keratoconjunctivitis caused by microsporidia (strong, very low).
• Oral albendazole can be considered in addition to topical therapy for keratoconjunctivitis due to microsporidia other than *E. bieneusi* and *V. corneae* (expert opinion).
II. In HIV-infected children who have been treated for microsporidiosis, when can treatment (secondary prophylaxis) be safely discontinued?
Clinicians may consider continuing treatment for microsporidiosis until improvement in severe immunosuppression is sustained (more than 6 months at Centers for Disease Control and Prevention immunologic category 1 or 2) and clinical signs and symptoms of infection are resolved (weak, very low).
Rating System:
Strength of Recommendation: Strong, weak
Quality of Evidence: High; Moderate; Low; or Very Low

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*: • Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily Ocular Infection: • 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: • 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: • Immune reconstitution may lead to microbiologic and clinical response. For Disseminated (Not Ocular) and Intestinal 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 (in addition to ART) *Treatment Duration:* • 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 For *E. bieneusi* or *V. corneae* Infections: • Fumagillin (where available) adult dose 20 mg by mouth 3 times daily, *or* • 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) For Ocular Infection: • 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) *Treatment Duration:* • 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) • 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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Mycobacterium avium Complex Disease

Updated: April 23, 2026
Reviewed: April 23, 2026

Panel's Recommendations

Primary Prevention of *Mycobacterium avium* Complex (MAC)

- Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV who have advanced immunosuppression, as defined by CD4 T lymphocyte (CD4) cell count below, and who are not on a fully suppressive antiretroviral (ARV) regimen (AIII). Disseminated MAC should be excluded prior to initiating prophylaxis.
  - *Children Aged <1 Year:* <750 cells/mm^3
  - *Children Aged 1–5 Years:* <500 cells/mm^3
  - *Children Aged ≥6 Years:* <200 cells/mm^3
- For children who cannot tolerate azithromycin or clarithromycin, rifabutin may be used despite concerns of drug interactions and lack of efficacy data in children (BIII).

Discontinuing Primary Prophylaxis

- Primary prophylaxis cannot be discontinued in children with HIV aged <2 years and should be discontinued in children with HIV ≥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 (AI*).

Treatment of MAC in Children With HIV

- Testing of all MAC isolates for susceptibility to clarithromycin or azithromycin, in addition to amikacin, linezolid, and moxifloxacin, is recommended (AIII).
- Combination therapy with a minimum of two drugs for ≥12 months (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (AIII). Monotherapy is associated with the emergence of high-level drug resistance.
- Clarithromycin is suggested as the preferred macrolide, although azithromycin is preferred by many experts because of better tolerance and fewer drug interactions (BIII).
- Some experts would add rifabutin as a third drug to the macrolide/ethambutol regimen (CIII), particularly in the absence of suppressive ART and in the presence of severe illness; however, with such combination therapy, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted (AIII). Ritonavir may increase the concentration of rifabutin and its active metabolite(s). Other experts recommend against the use of rifabutin as a third agent in children due to 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.
- In children with HIV and disseminated MAC disease who have no prior ART experience or are not receiving effective ART, ART should be started at the same time as antimycobacterial therapy (BII*). The regimens should be modified when there is potential for an adverse drug–drug interaction(s) between the ARV and antimycobacterial drugs (BII*).

Management of Treatment Failure

- Children who fail to respond clinically and have persistent mycobacteremia after 8–12 weeks of treatment should undergo repeat susceptibility testing of MAC isolates and should subsequently start a new multidrug regimen involving at least two drugs not previously used and to which the isolate is susceptible (AIII). Drugs that should be considered for this scenario include rifabutin (if not previously used), amikacin, ciprofloxacin, moxifloxacin, and/or bedaquiline (age 5 and older and at least 15 kg).

Secondary Prophylaxis

- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (AIII). Secondary prophylaxis typically consists of continued multidrug therapy used in the treatment of disease.
- 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; *and*
  - Remain asymptomatic for MAC; *and*
  - Receiving stable ART (i.e., ART not requiring change for virologic or immunologic failure); *and*
  - 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 [AII] and >200 cells/mm^3 for children aged 2 to <6 years [CII]).
- There are limited data to recommend discontinuation of secondary prophylaxis in children <2 years. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate (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 postpubertal adolescents

Epidemiology

Current molecular technologies have led to the identification of more than 200 species within the *Mycobacterium* genus. *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 and are not typically distinguished in the microbiology laboratory. Surveillance data continue to show an increasing rate of MAC infection in some regions within the United States, particularly among women and people aged 65 years or older.[1] Comprehensive updated guidelines on the treatment of nontuberculous mycobacterial diseases were published in 2020.[2] In the United States, NTM infections outnumber *Mycobacterium tuberculosis* infections and have become an important cause of pulmonary morbidity in adults.[3] In children not infected with HIV, it appears that the overall prevalence of NTM is increasing over time.[4,5] However, disseminated NTM is rare in immunocompetent children. The incidence of all opportunistic infections has decreased since the advent of effective ARTs, and prevalence remains significantly lower than the pre-ART era.[6]

Before the advent of ART, MAC was second only to *Pneumocystis jirovecii* pneumonia among opportunistic infections (OIs) in children with HIV in the United States. With the availability of ART, all OIs have continued to decrease in children with HIV.[7] The incidence of MAC has greatly decreased, from 1.8 episodes per 100 person-years in the pre-ART era to 0.14 per 100 person-years in the ART era.[8,9] MAC is ubiquitous in the environment and presumably is acquired by routine exposures through inhalation, ingestion, or inoculation.[10]

MAC can appear as isolated lymphadenitis in children with and without HIV. In children with HIV, disseminated MAC 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 children under the age of five with HIV than in older children or adults with HIV. MAC is a recognized complication of advanced immunologic deterioration among children with HIV.[9-11]

Clinical Manifestations

Respiratory symptoms are uncommon in children with HIV 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. Gastrointestinal symptoms can occur alone or in combination with systemic findings, including lymphadenopathy, hepatomegaly, and splenomegaly. 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.[12]

Diagnosis

Procedures used to diagnose MAC in children with HIV are the same as those used for adults with HIV. 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). Isolation of MAC from a cervical lymph node but with no evidence of dissemination (negative blood cultures) indicates infection without dissemination. Blood cultures are a sensitive and minimally invasive technique for diagnosing disseminated MAC, with >90% of diagnosed individuals recording positive blood cultures.[12,13] 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. General guidelines for blood volume are 1 mL for infants and 1 mL per year of age up to the adult volume of 10 mL. The 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. MAC isolates can also be rapidly identified by their mycolic acid patterns from the same samples by high-performance liquid chromatography, line probe assays, and 16s rRNA gene sequencing. Single and multigene sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry can also be used, although these techniques have differing ability to discriminate between species and subspecies and have variable costs. These diagnostic techniques may only be available at high-volume laboratories.[13-17]

Histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection in children with typical signs and symptoms, but culture is essential to (1) differentiate NTM from *M. tuberculosis*; (2) determine which NTM is causing infection, and (3) perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is most useful because clinical response is correlated with macrolide susceptibility. 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.[13-17]

Although detection of MAC in stool or the respiratory tract may precede disseminated disease, no data demonstrates a correlation between initiation of prophylaxis in people with detectable organisms at these sites and reduced risk of developing disseminated MAC. Therefore, there is no recommendation for routine testing of stool or respiratory specimens for the presence of MAC.

Prevention Recommendations

Preventing Exposure

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance.[1,17] Person-to-person transmission is not believed to occur for MAC.

Preventing First Episode of Disease

The most effective way to prevent disseminated MAC in children with HIV is to preserve immune function through the use of effective ART. With the advent of suppressive ART, few children require primary prophylaxis. Current recommendations in adults with advanced immunosuppression do not recommend primary prevention if ARVs are started unless the individual remains viremic and a fully suppressive regimen is not available (see Disseminated *Mycobacterium avium* Complex Disease in the Adult and Adolescent Opportunistic Infection Guidelines). Children with HIV who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the CD4 count thresholds for children who remain viremic on ART but have no options for a fully suppressive ART regimen **(AIII).** Before prophylaxis is initiated in at-risk children, disseminated MAC disease must be ruled out, which includes obtaining a blood culture for MAC **(AIII).**

Published data defining CD4 values below which primary prophylaxis should be initiated were developed before the era of effective ART and typically used CD4 percentages rather than absolute values. However, CD4 absolute values were published in 2014; these values were used to define immunosuppression in children with HIV by age and may be used to guide MAC prophylaxis.[18]

Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV who have advanced immunosuppression based on the CD4 thresholds below **(AIII).**

- *Children Aged <1 Year:* <750 cells/mm^3
- *Children Aged 1 to 5 Years:* <500 cells/mm^3
- *Children Aged ≥6 Years:* <200 cells/mm^3

Based on randomized controlled trials, clarithromycin and azithromycin are the preferred prophylactic agents for adults with HIV.[19-21] Although there are no randomized controlled trials in children, either clarithromycin and azithromycin is recommended for prophylaxis in children **(AIII);** 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 **(AIII).** 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 **(BIII).**

Based on both randomized controlled trials and observational data in adults with HIV, primary prophylaxis for MAC can be safely discontinued in children with HIV who respond to ART with an increase in CD4 count.[22,23] In a prospective study that evaluated the incidence of OIs after discontinuation of OI prophylaxis in 63 children with HIV with CD4 percentages ≥20% for those aged >6 years and ≥25% for those aged 2 to 6 years, no MAC events were observed at a median of 2 years of follow-up.[23]

Primary prophylaxis cannot be discontinued in children aged <2 years **(BIII)** but should be discontinued in children with HIV aged ≥2 years receiving stable ART for ≥6 months and experiencing sustained (>3 months) CD4 count recovery well above the age-specific target for initiation of prophylaxis **(AI*).**

Treatment Recommendations

Treating Disease

Disseminated MAC infection should be treated in consultation with a pediatric infectious disease specialist who has expertise in pediatric HIV.

In the United States, treatment with ART has become the standard practice for all children with HIV. The optimal time to start ART in previously untreated children who present with disseminated MAC is unknown, but recovery of the immune system is critical in controlling disseminated MAC. In such children, ART should generally be initiated at the same time as treatment for MAC. The regimens should be modified when there is potential for an adverse drug–drug interaction(s) between the antiretroviral and antimycobacterial drugs **(AIII).**

While waiting for identification and susceptibility results from diagnostic specimens, as well as immune system recovery, many experts will start an initial regimen of more than three drugs that are likely to be active against a broad range of mycobacteria (i.e., both *M. tuberculosis* and NTM), including ethambutol, azithromycin, and rifabutin, plus a fluoroquinolone and/or potentially an injectable aminoglycoside (e.g., amikacin). When specifically treating disseminated MAC, combination therapy with at least two active drugs (typically a macrolide plus ethambutol) and improving immunologic status with effective ART are cornerstones for controlling disseminated MAC disease.

Macrolide monotherapy results in emergence of high-level drug resistance within weeks.[24] Clarithromycin levels can be increased by protease inhibitors (PI) and decreased by the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin is generally preferred over clarithromycin because it is not metabolized as significantly by the cytochrome P450 (CYP) system; therefore, azithromycin can be used without major concern for significant drug interactions with PIs and NNRTIs. However, it is important to always perform a drug–drug interaction check and/or consult with a pharmacist.

There are no definitive data demonstrating improved survival after adding rifabutin to the typical macrolide plus ethambutol regimen.[25] However, this regimen may be considered in select pediatric patients with severe immunosuppression and widely disseminated MAC. Rifabutin is both a substrate and inducer of CYP3A4, which may lead to increased levels of nonboosted and boosted PIs.[25] This may warrant increased monitoring for drug toxicity when rifabutin and PIs are used together. Rifabutin should not be used with select integrase strand transfer inhibitors (INSTIs) because of a

significant reduction in therapeutic levels of these agents: bictegravir, once-daily elvitegravir, and injectable cabotegravir.[26] The INSTIs raltegravir, dolutegravir, and oral cabotegravir may be used without dose adjustment. Careful monitoring for appropriate response to ARV therapy and toxicity is important when using a rifabutin-containing regimen.

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 from a small unpublished study of 22 children with HIV (median age: 9 years) who received rifabutin in combination with two or more other antimycobacterial drugs for the treatment of MAC for 1 to 183 weeks were used by the U.S. Food and Drug Administration to create the product label; mean rifabutin doses ranged from 18.5 mg/kg for infants to 8.6 mg/kg for children aged 2 to 10 years, and reported adverse effects were similar to those reported in adults.[26] The most commonly reported dose in children has been rifabutin 5 mg/kg. Therapy is typically prolonged and depends upon response and immune reconstitution. Whether treatment success differs between rifampin versus rifabutin is unclear, although drug–drug interactions may be less significant with rifabutin.[27,28]

Testing of MAC isolates for susceptibility to clarithromycin or azithromycin, in addition to amikacin, moxifloxacin, and linezolid, is recommended **(AIII).**

Clarithromycin is recommended as the preferred macrolide, although azithromycin can be used as an alternative for children with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern **(BIII).**

Use of rifabutin as a third drug added to the macrolide plus ethambutol regimen is controversial **(CIII).** Pediatric studies are lacking, but one randomized controlled open-label study in adults compared clarithromycin plus ethambutol to clarithromycin plus rifabutin versus clarithromycin plus ethambutol plus rifabutin. Although the microbiologic response was similar, the three-drug arm had reduced macrolide resistance when relapse occurred.[33] Based on 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 severe illness. However, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy **(AIII).** Other experts recommend against using rifabutin as a third agent in children due to increased CYP450 activity. Guidelines and recommendations exist for dose adjustments necessary in adults treated with rifabutin and some components of ART regimens, but the absence of data in children precludes extrapolating these guidelines and recommendations to children with HIV undergoing treatment for disseminated MAC.[29] Pharmacokinetic data are available on the use of rifabutin with the boosted PI lopinavir/ritonavir in children with HIV/tuberculosis coinfection, which may be useful if rifabutin is considered.[29] Newer anti-mycobacterial agents, such as bedaquiline, have been used in adults for treatment of NTMs, but there are no data on use in children.[37]

Monitoring and Adverse Events

Clinically, most patients improve substantially during the first 4 to 6 weeks of therapy. Some experts would consider a repeat blood culture after 4 to 6 weeks of therapy for all children with an initial positive culture, regardless of clinical response to therapy. Fever improvement can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease, advanced immunosuppression, or failure to respond to ARV drugs, 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. Prolonged high-dose use of macrolides has been associated with hearing loss; however, there are no specific recommendations for routine hearing screening.[30] 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 relatively rare at doses of 15 mg/kg to 25 mg/kg in children with normal renal function. All children who are old enough to cooperate should undergo vision assessment prior to starting ethambutol and periodically during treatment. The risks and benefits of using ethambutol in very young children whose visual acuity cannot be monitored must be carefully considered.[31]

Children receiving clarithromycin plus rifabutin should be observed for rifabutin-related development of leukopenia, uveitis, polyarthralgia, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some children with HIV receiving rifabutin.[27]

Immune reconstitution inflammatory syndrome (IRIS) has been reported in adults and children with HIV receiving MAC therapy and ART.[32-35] 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 has occurred after initiating ART (unmasking IRIS). In addition, paradoxical worsening of systemic or local MAC symptoms may occur as the immune system is rapidly reconstituted. Mycobacteremia is typically absent. Children with moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) or, if unresponsive to NSAIDs, a short course (e.g., 4 weeks) of systemic corticosteroid therapy while continuing ART.

Managing Treatment Failure

Children who do not respond to therapy and either exhibit persistent symptoms or fail to record negative cultures are likely exhibiting 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 the event of MAC treatment failure. A new multidrug regimen adding two or more drugs not previously used and to which the isolate is susceptible should be administered **(AIII).** Macrolides remain the most effective agent for MAC and should be continued if the isolate remains susceptible. Drugs that should be considered for this scenario include rifabutin (if not already used), amikacin, linezolid, ciprofloxacin or moxifloxacin, and/or bedaquiline (age ≥5). [12,17]

Preventing Recurrence

There are no pediatric data regarding secondary prophylaxis for MAC infection. However, children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence **(CIII).** Many experts recommend clarithromycin plus ethambutol for secondary prophylaxis. Monotherapy with clarithromycin or azithromycin is associated with the development of high-level drug resistance.

Discontinuing Secondary Prophylaxis

In the era of combination ART, very few cases of invasive MAC have been reported, and recommendations for the discontinuation of secondary prophylaxis remain unchanged. On the basis of immune reconstitution data in adults[31,36] and data in children discontinuing primary prophylaxis, secondary prophylaxis should be discontinued in children with HIV who are aged ≥2 years and have completed ≥6 months of treatment for MAC, remain asymptomatic for MAC, are receiving stable ART (i.e., ART not requiring change for virologic or immune failure), and who have sustained (≥6 months) CD4 count recovery well above the age-specific targets for initiation of primary prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥6 years **[AII]** and >200 cells/mm^3 for children aged 2 years to <6 years **[BII]**). Multidrug secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

There are no data and limited clinical experience to guide the decision to discontinue secondary prophylaxis for children aged <2 years who have completed 1 year of treatment for disseminated MAC and who are receiving effective ART. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate **(CIII).** Consultation with a pediatric HIV expert is advised.

Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	• Clarithromycin[a] 7.5 mg/kg (maximum 500 mg/dose) PO twice daily, *or* • Azithromycin 20 mg/kg (maximum 1,200 mg) PO once weekly	• Azithromycin 5 mg/kg (maximum 250 mg) PO once daily • For children who cannot tolerate azithromycin or clarithromycin, rifabutin (5 mg/kg/daily, maximum dose 300 mg) is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use.	Primary Prophylaxis Indicated for Children With HIV Who Have Advanced Immunosuppression, as Defined by CD4 Count Below, and Who Are Not on a Fully Suppressive ARV Regimen • *Aged <1 Year:* CD4 count <750 cells/mm^3 • *Aged 1 to 5 Years:* CD4 count <500 cells/mm^3 • *Aged ≥6 Years:* CD4 count <200 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis • Do not discontinue in children aged <2 years. • After ≥6 months of ART, *and* o *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for >3 consecutive months o *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for >3 consecutive months

Indication	First Choice	Alternative	Comments/Special Issues
			Criteria for Restarting Primary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3
Secondary Prophylaxis (Chronic Suppressive Therapy)	• See initial treatment below. • *For Children Aged ≥6 Years Who Received Rifabutin as Part of Initial Treatment:* rifabutin[a] 5 mg/kg (maximum 300 mg) PO once daily with food	• Azithromycin 5 mg/kg (maximum 250 mg) PO once daily, *plus* • Ethambutol 15–25 mg/kg (maximum 2.5 g) PO once daily, with or without food • Children aged ≥6 years who received rifabutin as part of initial treatment: rifabutin 5 mg/kg (maximum 300 mg) PO once daily with food	Secondary Prophylaxis Indicated • Prior disease Criteria for Discontinuing Secondary Prophylaxis • Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence. • There are limited data to recommend discontinuation of secondary prophylaxis in children aged <2 years. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate. *Fulfillment of All of the Following Criteria* • Completed ≥6 months of stable ART, *and* • Completed ≥12 months of MAC therapy, *and* • Asymptomatic for signs and symptoms of MAC, *and either* • *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for ≥6 consecutive months, *or* • *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for ≥6 consecutive months Criteria for Restarting Secondary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Initial Treatment (≥2 Drugs): • Clarithromycin[a] 7.5–15 mg/kg (maximum 500 mg/dose) PO twice daily, *plus* • Ethambutol 15–25 mg/kg (maximum 2.5 g/day) PO once daily followed by chronic suppressive therapy *If Experiencing Severe Disease (Extensive End Organ Involvement, Prolonged Symptoms, Slow Response to Therapy)* • Add rifabutin[a] 10–20 mg/kg (maximum 300 mg/day) PO once daily	If Intolerant to Clarithromycin • Azithromycin 10–12 mg/kg (maximum 500 mg/day) PO once daily, plus ethambutol For Children With Severe Symptoms or Disseminated Disease Who Need a Rifabutin Alternative or a Fourth Drug to Supplement a Macrolide/ Ethambutol/Rifabutin Regimen • Amikacin[b] 15–30 mg/kg (maximum 1.5 g/day) IV in one or two divided doses. Therapeutic drug monitoring (peak and trough levels) is required, *or* • Linezolid 10 mg/kg/dose PO every 8 hours for age 1 month to <12 years (maximum 600 mg/dose) and 10 mg/kg/dose PO every 12 hours (maximum 600 mg) for age ≥12 years, *or* • Moxifloxacin 7.5–10 mg/kg (maximum dose 400 mg daily) PO once daily, *or* • Levolfoxacin 15-20 mg/kg/dose PO once daily (maximum dose 750 mg), *or* • Ciprofloxacin 10–15 mg/kg (maximum 1.5 g/day) PO twice daily, *or* • Bedaquiline for children aged ≥5 years weighing ≥15 kg (based on MDR-TB regimens): o *Weeks 1–2:* 400 mg once daily o *Weeks 3–24:* 200 mg three times weekly o For therapy beyond 24 weeks, consider consultation with a pediatric infectious disease/HIV expert.	Susceptibility testing is recommended prior to treatment initiation. Combination therapy with a minimum of two drugs is recommended for ≥12 months. Careful monitoring for drug–drug interactions is advised. Clofazimine is associated with increased mortality in adults with HIV and should not be used. Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination. Fluoroquinolones (e.g., ciprofloxacin and moxifloxacin) are used with caution 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. Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. Limited data for bedaquiline in adults with NTM.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenous; MAC = *Mycobacterium avium* complex; MDR-TB = multidrug-resistant tuberculosis; NTM = nontuberculous mycobacteria; PO = orally

[a] Careful monitoring of drug–drug interactions is critical when using rifabutin or clarithromycin in children on ARVs.

[b] Amikacin levels for therapeutic drug monitoring: peak (C_{max}) 30–40 mg/L and trough (C_{min}) <5 mg/L for once daily dosing; C_{max} 65–80 mg/L for thrice weekly dosing

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Mycobacterium tuberculosis

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

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 (≥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-programs/php/about/tb-coe.html
- 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 *Also Known as TB Preventive Therapy*	Source Case Drug Susceptible *Age 2 to <12 years* • 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) *Age ≥12 years* • 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) Source Case Drug Resistant • For isoniazid-resistant source cases, daily rifampin 15–20 mg/kg (maximum 600 mg/day) for 4 months is recommended. • 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 *or* Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 15–20 mg/kg (maximum 600 mg/day) for 3 months duration *or* Isoniazid 10–15 mg/kg (max 300 mg) daily for 6–9 months	Indications • Positive TST (TST ≥5 mm in children with HIV) or IGRA without previous TB treatment • Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis) Considerations • TB disease must be excluded before starting treatment for latent TB infection. • Drug-drug interactions with ART should be considered for all rifamycin-containing alternatives. Criteria for Discontinuing Prophylaxis • Only with documented severe adverse event, such as hepatotoxicity, hypersensitivity, or other adverse drug reactions, which are rare in children and adolescents. Adjunctive Treatment • 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 girls and women.

Dosing Recommendations for Preventing and Treating TB in Children with HIV

Indication	First Choice	Alternative	Comments/Special Issues
Treatment of TB Disease	Intrathoracic Disease *Drug-Susceptible TB* • Intensive Phase (2 Months) o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily, plus o Pyrazinamide 30–40 mg/kg body weight (maximum 2 g/day) by mouth once daily, plus o Ethambutol 15–25 mg/kg body weight (maximum 1 g/day) by mouth once daily o In children with minimal disease with fully drug-susceptible TB, some experts recommend a three-drug intensive phase regimen excluding ethambutol. • Continuation Phase (4 Months) o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily Extrathoracic Disease Note: Depends on disease entity • Lymph node TB—treat as minimal intrathoracic disease • Bone or joint disease—consider extending the continuation phase to 10 months (for total duration of therapy of 12 months).	Alternative for Rifampin • Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if three times a week) • Discuss with an expert. Alternative Continuation Phase with Three Times Weekly Dosing *If Good Adherence and Treatment Response (4 months)* • Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth three times per week, plus • Rifampin 15–20 mg/kg body weight (maximum 600 mg/day) three times per week • 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. If ART-naive, start TB therapy immediately and initiate ART within 2 to 8 weeks. If already on ART, review regimen to minimize potential toxicities and drug interactions; start TB treatment immediately. Potential drug toxicity and interactions should be reviewed at every visit. Drug interactions with ART should be considered for all rifamycin-containing alternatives. Adjunctive Treatment • Co-trimoxazole prophylaxis • 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 girls and women. • 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 • 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. • 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. • Consider extending the continuation phase to 10 months (for a total duration of therapy of 12 months). • Discuss with an expert. Drug-Resistant TB • 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 • 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 Pneumonia

Updated: December 22, 2025
Reviewed: December 22, 2025

Panel's Recommendations

Prevention of Primary Exposure

- At-risk immunocompromised patients should not share a room with a patient who has known *Pneumocystis* pneumonia (PCP) or an undiagnosed respiratory tract infection (**strong**, **low**).

Primary Prophylaxis

- PCP prophylaxis is recommended for all children with HIV with stage 3 CD4 T lymphocyte (CD4) cell count (**strong**, **moderate**):
  - Aged ≥6 years: CD4 count <200 cells/mm^3 or CD4 percentage <14% if CD4 count is unavailable
  - Aged 1 year to <6 years: CD4 counts <500 cells/mm^3 or CD4 percentages <22% if CD4 count is unavailable
- For infants, PCP prophylaxis is recommended beginning at age 4–6 weeks and continuing until age 12 months, regardless of CD4 count or percentage (**moderate**, **low**). At age 12 months, infants should be reassessed based on the CD4 count or percentage thresholds above (**moderate**, **low**).
- PCP prophylaxis should also be considered in infants with perinatal HIV exposure if HIV infection cannot be presumptively excluded by 4–6 weeks of age (**strong**, **low**). Prophylaxis should be continued until HIV infection can be presumptively excluded.
- HIV infection may be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks and one at age ≥4 weeks) or one negative virologic test at age ≥8 weeks at least 2 weeks after discontinuing multidrug antiretroviral (ARV) prophylaxis/presumptive therapy. In breastfed infants of individuals on antiretroviral therapy (ART) with sustained viral suppression and ongoing close monitoring, the risk of postnatal HIV transmission is extremely low (<1%). In this context, the benefits of trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole) are unlikely to outweigh its risks, and most experts would not administer PCP prophylaxis for breastfed infants otherwise meeting the above criteria for negative virologic testing.
- TMP-SMX administered daily or 3 days/week (either consecutively or on alternating days [e.g., Monday, Wednesday, Friday]), is the drug of choice for PCP prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum (**strong**, **high**).
- For children with HIV who are unable to take TMP-SMX, atovaquone (**strong**, **high**) or dapsone (**strong**, **moderate**) is recommended.
- Intravenous (IV) or aerosolized (for children old enough to use Respirgard II nebulizer) pentamidine administered monthly can be used for children unable to take TMP-SMX, atovaquone, or dapsone (**strong**, **moderate**). Of note, atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Discontinuing Primary Prophylaxis

- Discontinuation of PCP prophylaxis is recommended for children with HIV who have received stable ART for ≥6 months and meet the following age-specific criteria for >3 consecutive months (**strong**, **moderate**):
  - Aged ≥6 years: CD4 count ≥200 cells/mm^3, or CD4 percentage ≥14% if CD4 count unavailable
  - Aged 1 to <6 years: CD4 count ≥500 cells/mm^3, or CD4 percentage ≥22% if CD4 count unavailable
- Discontinuation of PCP prophylaxis can be considered in patients aged ≥6 years who have had an undetectable viral load for >6 months with a CD4 count 101 to 200 cells/mm^3 and are intolerant of prophylaxis medications (**weak**, **low**).

Panel's Recommendations
• CD4 count and CD4 percentage should be reevaluated every 3–4 months until stabilized, and according to HIV treatment guidelines thereafter. Prophylaxis should be reinstituted if the age-specific criteria for prophylaxis are reached (strong, low). Treatment • IV TMP-SMX is the recommended initial treatment for PCP (strong, high). o As the acute pneumonitis subsides, children with mild-to-moderate PCP 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 (strong, low). • IV pentamidine isethionate once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5–7 days of TMP-SMX therapy (strong, moderate). Daily IV pentamidine is associated with significant adverse effects (such as renal dysfunction and electrolyte and glucose abnormalities) and requires close monitoring. Allergy consultation and desensitization to TMP-SMX when appropriate should be attempted prior to initiating IV pentamidine. Atovaquone is a suitable alternative for patients with mild-to-moderate PCP (weak, low). • Ideally starting within 72 hours of diagnosis, a 21-day tapering course of corticosteroids is recommended in cases of moderate-to-severe PCP (defined as PaO_2 <70 or alveolar-arterial gradient ≥35 mmHg) (strong, moderate). Secondary Prophylaxis • Children with HIV who have experienced an episode of PCP should continue PCP prophylaxis after completion of treatment until their CD4 counts exceed the threshold for initiating prophylaxis, using criteria described for discontinuation of primary prophylaxis (strong, high). • Children who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite having normal or high CD4 counts or percentages (strong, moderate).
Rating System *Strength of Recommendation:* Strong; Weak *Quality of Evidence:* High; Moderate; Low; Very Low

Epidemiology

Pneumocystis spp. are found worldwide in the lungs of humans and other animals. The organisms are host-specific, and cross-infection between humans and other species does not occur. *Pneumocystis* spp. from all sources are 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 taxonomy have occurred, including a designation of *P. carinii* exclusively for rat-specific species and *Pneumocystis jirovecii* for human-specific species. *Pneumocystis* has been designated a fungus based on DNA analysis, but it has several biologic features of protozoa. Most humans are infected with *Pneumocystis* early in life. Most children acquire *Pneumocystis* antibodies by age 13, and in some cases, the rate reaches as high as 85% among children aged ≤2 years.[1-3] Immunocompetent infants with the infection are either asymptomatic or have mild respiratory symptoms. *Pneumocystis* pneumonia (PCP) occurs almost exclusively in the immunocompromised host.

Data from the Centers for Disease Control and Prevention Pediatric Spectrum of Disease Project (1994–2001) indicated a decline in PCP rates (cases per 1,000 children with HIV) from 25 in 1994 to <10 in 2001.[4] This decline probably resulted from the introduction of antiretroviral therapy (ART) in

children with HIV in 1995, as well as chemoprophylaxis for PCP. An analysis of PCP-related diagnostic codes from the Kids' Inpatient Database (abbreviated as KID) similarly showed a 65% decrease in the rate of pediatric PCP from 1997 to 2012, with most of the decline seen in children with HIV and stable rates of PCP among children with other immunocompromising conditions.[5] However, PCP remains an important AIDS-indicator disease among children with HIV. For instance, it was the top AIDS-indicator disease in children with perinatally acquired HIV through 2009 in the Ukraine European Collaborative Study Group, 44% of whom had started ART at a median of age 18 months.[6] The Pneumonia Etiology Research for Child Health (PERCH) study also identified *P. jirovecii* as the most common etiology of pneumonia in South African and Zambian children with HIV younger than 5 years of age from 2011 to 2013.[7,8] The highest incidence of PCP in children is in the first year of life, with the number of cases peaking at ages 3 to 6 months.[9-11] PCP is a major cause of death among infants and children with HIV in low- and middle-income countries. Autopsies done in Africa revealed PCP in 16% of children who died with HIV or AIDS during 1992 and 1993,[12] and in 44% of those who died during 2000 and 2001.[13] A 2024 meta-analysis that included 11 worldwide studies on patients of all ages with HIV found a 52% higher mortality rate among patients with PCP than those without PCP diagnosed (odds ratio 1.522, 95% confidence interval [CI] 0.959–2.416).[14]

The mode of transmission of *Pneumocystis* among infants, children, and adults with HIV is not firmly established, but airborne human-to-human transmission is likely. Animal studies show *Pneumocystis* is transmitted by air from infected rats to susceptible rats[15,16] and from immunocompetent mice with subclinical infection to immunocompromised mice.[17] Human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases.[18-20]

The primary determinant of susceptibility to PCP in patients with HIV, regardless of age, is cell-mediated immunity status. Severe immunocompromise, 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. These guidelines apply only to PCP prevention and treatment in children with HIV. The risk factors for developing PCP are less clear in other states of immunodeficiency, and therefore the criteria for implementing prophylaxis and considering infection do not necessarily apply to other patient groups.

Clinical Manifestations

Prominent clinical features of PCP among children with HIV are fever, tachypnea, dyspnea, and cough. The severity of these signs and symptoms varies from child to child. Onset can be abrupt or insidious and may include nonspecific symptoms, such as poor feeding, diarrhea, or weight loss. Some patients may not be febrile, but almost all will have tachypnea by the time pneumonitis is evident via chest radiograph. Physical examination sometimes shows bilateral basilar rales with evidence of respiratory distress and hypoxia.

In children with HIV hospitalized with pneumonia, four clinical variables are independently associated with PCP: age <6 months, respiratory rate >59 breaths per minute, hypoxia (arterial percentage hemoglobin saturation ≤92%), and absence of vomiting.[21] A high plasma HIV RNA concentration strongly predicts PCP and other opportunistic infections.[22]

Extrapulmonary *Pneumocystis* organisms, often associated with a localized inflammatory reaction, are found in <2.5% of adults and children with HIV.[23,24] Extrapulmonary pneumocystosis can occur without concurrent PCP and can be located at multiple noncontiguous sites. Involved sites have included the ear, eye, thyroid, spleen, gastrointestinal (GI) tract, peritoneum, liver, and pancreas.

Less frequently involved sites include the 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 mmHg) and an alveolar-arterial gradient >30 mmHg. CD4 percentages are often <14% and CD4 counts are usually <200 cells/mm^3 in children aged 6 years and older. Lactate dehydrogenase is often increased, but this finding is not specific to 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 are observed, as well as occurrences of pneumothorax or pneumomediastinum. Coinfection with other organisms, such as cytomegalovirus or pneumococcus, has been reported in children with HIV.[11,25,26] Children with dual infections may have more severe disease.

A definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids in the presence of pneumonitis. Diagnostic procedures for suspected PCP are the same for children as for adults (see the *Pneumocystis* Pneumonia section of the Adult and Adolescent Opportunistic Infection Guidelines), but some procedures may be more difficult to perform in children. Optimal specimens for diagnosis of PCP should be obtained from the bronchial tree and include bronchoalveolar lavage fluid, tissue from transbronchial or open lung biopsy, or induced sputum. Induced sputum analysis, however, has reduced sensitivity and may be difficult in children aged <2 years because of their small airways and poor ability to produce sputum. Additional specimens, such as non-induced sputum, oral secretions, or nasogastric aspirates, can be helpful if positive but have significantly lower sensitivity and should not be used to exclude the diagnosis.[27]

Various stains can be used to identify *Pneumocystis* organisms in specimens. Gomori methenamine-silver and toluidine blue stain the cyst wall. Giemsa, Diff-Quick, and Wright stains depict the trophozoites and intracystic sporozoites but do not stain the cyst wall. Direct immunofluorescent staining should be used in conjunction with stains to detect cysts and trophozoites.[28,29]

Demonstration of the organism by polymerase chain reaction (PCR) is being used more frequently to diagnosis PCP. It is widely available at many major medical centers, generally considered to be more sensitive than staining methods and requires, less expertise. However, its high sensitivity makes PCR more likely to detect colonization than traditional staining methods. The significance of colonization has yet to be determined. The utility of quantitative PCR in monitoring treatment response has not been established.[28,29]

Several serologic biomarkers have been evaluated as adjunctive non-invasive testing strategies for diagnosing PCP in adults with HIV with pulmonary symptoms, including (1→3)-beta-d-glucan (BG), lactate dehydrogenase, procalcitonin, S-adenosyl methionine, and Krebs von den Lungen-6 antigen (KL-6). BG has a high sensitivity (above 90%) in adults with HIV. However, BG and the other biomarkers listed are nonspecific and are also elevated in the presence of other fungal infections and medications. Combined BG and KL-6 testing had the highest accuracy, with sensitivity and specificity approaching 95% and 90%, respectively, in one European study.[30-32] Mildly elevated serum BG levels have also been detected in a case series of immunocompetent

infants suspected of having primary *Pneumocystis* infection, as well as in several children with PCP and underlying hematologic malignancies.[33,34]

Prevention Recommendations

Preventing Exposure

Clinical data upon which to make a decision regarding isolation of patients with PCP are limited. However, animal model experiments suggest that transmission occurs easily,[35] and the organism has been detected in the air around patients with PCP.[36] Additionally, a study in France and Switzerland identified person-to-person transmission of PCP as the cause for increased rates of trimethoprim-sulfamethoxazole (TMP-SMX) resistant strains.[37] Furthermore, molecular analyses of PCP case clusters in solid organ and hematopoietic stem cell transplant recipients reveal that human-to-human transmission has occurred in nosocomial outbreak settings.[38-43] Immunocompromised patients who are adherent with PCP prophylaxis, especially with TMP-SMX, are unlikely to acquire PCP. However, providers should avoid placing at-risk patients in a room with another patient with PCP or an undiagnosed respiratory tract infection **(strong, low).** 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. This is especially true of respiratory illnesses occurring during the first 2 years of life, in which up to 85% of children acquire 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.[44] Prophylaxis is recommended for all children with HIV meeting stage 3 classification by CD4 counts (or by CD4 percentages, if counts are not available). This includes children aged ≥6 years with CD4 counts <200 cells/mm^3 or CD4 percentage <14%, and children aged 1 years to <6 years with CD4 counts <500 cells/mm^3 or CD4 percentage <22% **(strong, moderate).** PCP chemoprophylaxis is also recommended for all infants with HIV beginning at age 4 to 6 weeks of age and continuing until 12 months of age regardless of CD4 count or percentage **(moderate, low).** CD4 cell counts can decrease rapidly in infants with HIV and may not be a useful marker to determine PCP susceptibility in the first year of life.[45] These data were obtained during a time when perinatal transmission was high and combination ART was not available. A recent observational study (IMPAACT P1115) now indicates that infants started on very early ART can maintain high CD4 counts throughout infancy; however, more studies are needed to validate the low risk of PCP in infants who receive early ART.[46]

PCP remains a top AIDS-defining illness in infants and children with perinatally-acquired HIV worldwide. It has a peak incidence during the first year of life with a marked increase starting around 2 months of age. Initial guidelines recommended initiating PCP prophylaxis in perinatally-exposed infants based on CD4 count threshold. CD4 T lymphocytes, however, can decrease rapidly in infants with HIV, making it impractical to monitor closely enough to start prophylaxis in time.[45] Young infants with poorly controlled HIV can also be at risk for PCP regardless of CD4 count. In a study conducted from 1991 to 1993, 18% of children aged less than 12 months in the United States did not receive diagnostic testing.[45]

PCP prophylaxis should be considered in infants with perinatal HIV exposure regardless of CD4 count or percentage if HIV infection cannot be presumptively excluded by 4 to 6 weeks of age **(strong, low).** Prophylaxis should be continued until HIV infection can be presumptively excluded.

Most infants born in the United States who are exposed to HIV will have HIV infection presumptively excluded by this time if current virologic assay diagnostic testing recommendations are followed. HIV infection may be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks and one at age ≥4 weeks) or one negative virologic test at age ≥8 weeks at least 2 weeks after discontinuing multidrug ARV prophylaxis/presumptive therapy. In infants breastfed by mothers on ART with sustained viral suppression and ongoing close monitoring, the risk of postnatal HIV transmission is extremely low (<1%). In this context, the benefits of TMP-SMX are unlikely to outweigh its risks, and most experts would not administer PCP prophylaxis for breastfed infants otherwise meeting the above criteria for negative virologic testing. Infants with HIV should be administered prophylaxis until age 1 year, at which time they should be reassessed based on the age-specific CD4 count or percentage thresholds mentioned above **(moderate, low).**

The Preventing HIV Transmission During Infant Feeding section of the Pediatric Antiretroviral Guidelines reviews evidence supporting the low risk of postnatal HIV transmission during breastfeeding with sustained viral suppression and recommendation to discontinue breastfeeding when HIV RNA is ≥200 copies/mL. There is no consensus regarding the management of infants who are breastfed, despite persistent maternal viremia due to lack of strong evidence base. Some experts would initiate presumptive HIV therapy for these infants and consider initiating PCP prophylaxis, particularly in the absence of close monitoring.

TMP-SMX (cotrimoxazole) is the drug of choice for PCP prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(strong, high).**[47-49] TMP alone has little, if any, anti-*Pneumocystis* activity, but it enhances the activity of the sulfonamide (SMX). The prophylactic dosage of TMP-SMX is calculated based on the trimethoprim (TMP) component: TMP 5 to 10 mg/kg body weight per day (maximum dose: 320 mg) or TMP 150 mg/m^2 body surface area per day (maximum dose: 1,600 mg). TMP-SMX is administered orally as either (1) a single daily dose[50] or (2) divided every 12 hours on 3 consecutive days per week[51] or on alternate days (e.g., Monday, Wednesday, Friday). Alternative dosing schedules, such as twice weekly[52-54] or once weekly,[55] have been used successfully in pediatric oncology patients at risk for PCP. In patients with impaired renal function, a reduced dose may be necessary. The use of TMP-SMX in infants younger than 2 months and premature infants is limited due to the risk of bilirubin displacement. Although TMP-SMX may be considered for short-duration treatment courses while closely monitoring bilirubin levels, this is impractical for indefinite prophylaxis periods. The potential benefits of use in this patient population must be carefully weighed against the potential risk of kernicterus, as well as the feasibility of close laboratory monitoring. TMP-SMX, preferably given daily, is also effective in preventing toxoplasmosis[56] and some bacterial infections (e.g., *Salmonella*, *Haemophilus*, *Staphylococcus*).[50,57-59]

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.[60] 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.[61,62]

Other effective and safe PCP prophylaxis regimens are available for patients unable to take TMP-SMX. However, many patients can safely resume TMP-SMX after resolution of a mild reaction. See

the Monitoring and Adverse Events section for further details and potential adverse reactions to the alternative agents discussed below.

Recommended alternatives include atovaquone[63] **(strong, high)** or dapsone[48] **(strong, moderate).** Atovaquone, formulated as a yellow oral suspension, is administered with food as a single daily dose.[48,49] Dapsone can be administered orally on a daily or weekly schedule.[64] In patients with HIV who cannot tolerate trimethoprim and/or sulfonamides, atovaquone and dapsone were similarly effective.[48] However, atovaquone is a more expensive alternative; dapsone is inexpensive but associated with more serious adverse effects than atovaquone. Additionally, unlike TMP-SMX and dapsone, atovaquone has no antibacterial activity but is effective against *Toxoplasma gondii*. Approximately two-thirds of patients intolerant to TMP-SMX can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or monthly aerosolized pentamidine but slightly less effective than TMP-SMX.[48,65] Children should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting dapsone to avoid a potential hemolytic reaction.

Intravenous (IV) or aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone **(strong, moderate).** It has the benefit of monthly administration but carries logistical consideration. IV pentamidine given monthly has been effective in preventing PCP in four retrospective cohorts of pediatric oncology patients. The initial concern regarding its effectiveness in children ages <2 years has been addressed in three subsequent studies.[66-69] If aerosolized pentamidine is considered, children must be developmentally capable of demonstrating proper inhalation technique and maintaining a tight seal on the mouthpiece to effectively use the Respirgard II nebulizer.[44] Dosing in young children (age up to 5 years) is not well established, and compliance with the nebulizer can be difficult.[70,71] Care should be taken to limit health care personnel exposure to the nebulized medication. Atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Discontinuing Primary Prophylaxis

Studies of adults and children with HIV following immune reconstitution after receipt of ART demonstrate acceptably low risks for PCP after discontinuation of prophylaxis.[72-77] The Pediatric AIDS Clinical Trials Group (PACTG) 1008 study enrolled 235 children and adolescents with HIV on antiretroviral therapy who received PCP prophylaxis for ≥6 months. Age-specific CD4 percentage criteria for enrollment were ≥20% for participants over age 6 years and ≥25% for those aged 2 to 6 years. PCP prophylaxis was discontinued at study entry.[72] 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 discontinuing prophylaxis in children who have achieved immune reconstitution. A single randomized controlled trial (RCT) and several prospective cohort studies in adults with HIV receiving ART demonstrated that PCP prophylaxis can be safely discontinued—with a breakthrough infection rate of 1.57 per 1,000 person-years—if plasma HIV RNA remains undetectable for at least 6 months, even in the absence of full immune reconstitution. This approach, however, has not yet been demonstrated in children with HIV.[78-82] Discontinuation of PCP prophylaxis is recommended for children with HIV who have received stable ART for ≥6 months and meet the following age-specific criteria for >3 consecutive months **(strong, moderate)**:

- Aged ≥6 years: CD4 count ≥200 cells/mm^3, or CD4 percentage ≥14% if count unavailable
- Aged 1 to <6 years: CD4 count ≥500 cells/mm^3, or CD4 percentage ≥22% if count unavailable

Discontinuation of PCP prophylaxis can be considered in children aged ≥6 years who have had undetectable viral load for >6 months with CD4 count 101 to 200 cells/mm^3 and are intolerant of prophylaxis medications **(weak, low).** CD4 percentage and CD4 count should be reevaluated every 3 to 4 months until stabilized, and according to HIV treatment guidelines thereafter. Prophylaxis should be reinstituted if the age-specific criteria for prophylaxis are reached **(strong, low).**

PCP prophylaxis should not be discontinued in infants with HIV aged <1 year despite immune reconstitution. Studies conducted prior to the availability of combination ART demonstrated that CD4 cell counts may not be a useful marker of PCP susceptibility in these infants, and more evidence is needed among infants who receive early ART to determine if PCP prophylaxis can be safely discontinued in the first year of life.[45,46]

Treatment Recommendations

Treating Disease

Intravenous TMP-SMX is the recommended treatment for PCP in children with HIV **(strong, high).** Although it has not been studied prospectively in children with HIV, studies from animal models and children with cancer indicate that TMP-SMX and pentamidine have equivalent microbiologic effects. However, the toxicities associated with pentamidine make TMP-SMX the preferred treatment.[47,83,84] Effective therapeutic trimethoprim serum concentrations of 5 to 10 µg/mL can be reached with the recommended dose administered orally in children with HIV.[85] As the acute pneumonitis subsides, children with mild-to-moderate PCP 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 **(strong, low).**

Adverse reactions to TMP-SMX are less frequent in children than in adults, and continuation of TMP-SMX is preferred when possible. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided, and allergy consultation for TMP-SMX desensitization in the case of hypersensitivity reactions is recommended. TMP-SMX should be stopped permanently following a life-threatening reaction and listed as an allergy in the patient electronic medical record. See the Monitoring and Adverse Events section for further details and potential adverse reactions to the alternative agents discussed below.

Intravenous pentamidine isethionate once daily is recommended for patients with severe PCP who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy **(strong, moderate).** Atovaquone can be used for treatment of mild-to-moderate PCP in patients unable to take TMP-SMX and for whom IV pentamidine is not tolerated or impractical to administer **(weak, low).**[86-89]

Daily intravenous pentamidine is associated with significant adverse effects, including renal dysfunction and electrolyte and glucose abnormalities, and therefore requires close monitoring of electrolytes and kidney function. Allergy consultation and desensitization to TMP-SMX, when appropriate, should be attempted prior to initiating intravenous pentamidine. Combining TMP-SMX with intravenous pentamidine is not recommended, as there is no evidence of enhanced efficacy from the combination, and it may increase the risk of toxicity.[71,77] In patients with clinical improvement after 7 to 10 days of IV therapy with pentamidine, experts consider it reasonable to transition to an oral regimen (i.e., atovaquone alone) to complete a 21-day course of therapy.

Atovaquone, dapsone in combination with trimethoprim, or clindamycin in combination with primaquine can be considered for treating mild-to-moderate PCP in patients unable to take TMP-SMX or pentamidine, but data on their use in children are lacking **(weak, low).** Atovaquone is an alternative for treatment of mild-to-moderate PCP in adults.[48,83,90] Dosing is age-dependent (see the Dosing Recommendations table). The bioavailability of atovaquone is approximately three times greater when taken with food than without food. Coadministration of atovaquone and rifampin is not recommended; atovaquone may increase the serum concentration of rifampin, and rifampin may decrease atovaquone concentration. Coadministration with rifabutin should also be avoided and both drug concentrations may decrease.

Dapsone in combination with trimethoprim is effective in treating mild-to-moderate PCP in adults.[91] Data on the combination's toxicity and efficacy among children are limited. Dapsone alone is less effective than the combination.[92] Clindamycin combination with primaquine has been found to be effective in treating mild-to-moderate PCP in adults. Both combinations can be considered as an alternative therapy for PCP in children despite lack of pediatric data. Primaquine is contraindicated in patients with G6PD deficiency because of the possibility of inducing hemolytic anemia. Dosing information for treating PCP is available only for adults. Dosing for children is based on use of these drugs for treating other infections.

On the basis of studies in both adults[93-99] and children,[100,101] a 21-day tapering course of corticosteroids is recommended in cases of moderate-to-severe PCP, generally defined as a PaO_2 value of <70 mmHg or an alveolar-arterial gradient of ≥35 mmHg **(strong, moderate).** If used, corticosteroids should be ideally started within 72 hours of diagnosis, as data are limited regarding benefit of steroids beyond this timepoint. A 2015 Cochrane review identified six high-quality RCTs evaluating the use of adjunctive corticosteroid treatment in PCP, including one study conducted in infants. This meta-analysis found that, among adults receiving ART, it would take at least 23 patients receiving adjunctive corticosteroid treatment to prevent one death from PCP. Additionally, patients who received corticosteroids had a relative risk of death of 0.59 (95% CI, 0.41–0.85) at 3 to 4 months after acquiring PCP. The randomized placebo-controlled trial of moderate quality that included 100 infants exposed to HIV in South Africa with clinical suspicion of PCP demonstrated a nonsignificant trend toward improved survival with adjunctive corticosteroid use.[101] Retrospective pediatric reviews and case series have indicated reduced acute respiratory failure, decreased need for ventilation, and decreased mortality with early use of corticosteroids in children with HIV who have PCP.[100,102,103] Corticosteroid doses for children varied between studies.

Some case reports have documented improved pulmonary function following surfactant administration in cases of severe disease such as respiratory distress syndrome with established respiratory failure requiring mechanical ventilation.[104-106] Alterations in surfactant function and composition have been demonstrated in adults with HIV and PCP.[107] 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.[108] Clinical improvement is observed at approximately 4.5 ± 2.5 days after initiation of treatment whereas radiographic improvement is not seen until approximately 7.7 ± 4.5 days.[108] Adverse events during treatment of *Pneumocystis* infection may occur as a result of immune reconstitution inflammatory syndrome (IRIS) or as adverse reactions to *Pneumocystis* treatment medications. IRIS is an antigen-driven inflammatory response secondary to

reconstitution of the immune system that can occur in response to ART initiation during an active infection. *Pneumocystis* infection is an infrequent cause of IRIS (1/44 [2.3%] of adults with IRIS) in adults and children with HIV.[109] Symptoms can mimic or worsen that of the initial infection with fever, cough, shortness of breath, and worsening radiographic findings. 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).[110,111] The overall frequency of adverse reactions appears to be lower in children with HIV than in adults; approximately 15% of children have substantial adverse reactions to TMP-SMX.[74] Data from a PACTG study of children with HIV 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.[63] None were fatal or irreversible reactions. Some very mild reactions will resolve without stopping the medication, and continuing treatment is preferred when safe to do so. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. On the basis of adult randomized clinical trials, unless the reaction has been life-threatening (e.g. SJS), TMP-SMX can be resumed in children after the reaction has resolved, preferably by beginning with low desensitizing daily doses and gradually increasing to therapeutic dosing.[112,113] In adults, 75% of patients affected tolerated re-challenge with TMP-SMX.[113] If a life-threatening reaction such as SJS occurs, TMP-SMX should be discontinued and not readministered.[110,111,113] See sections above for alternative prophylaxis and treatment options.

The most common adverse drug reaction to pentamidine isethionate is renal toxicity, which usually occurs after 2 weeks of therapy and can be avoided by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if the drug is 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 for PCP treatment.[114] This medication should not be administered with other nephrotoxic medications (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) or with agents associated with pancreatitis.

With dapsone and TMP, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemoglobinemia, anemia, and thrombocytopenia.[91,92] Dapsone is the problematic component of the combination and accounts for most of the adverse reactions.[65] Skin rashes (10% to 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, during the first 3 to 5 days of antibiotic therapy, a temporary worsening of symptoms may occur due to an inflammatory reaction caused by the antibiotic-induced killing of bacteria in the lungs. Therefore, an adequate trial of therapy is needed before switching medications due to 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.[115,116] Combining TMP-SMX with intravenous pentamidine is not recommended, as there is no evidence of enhanced efficacy from the combination and it may increase the risk of toxicity.[71,77]

Preventing Recurrence

None of the medications administered to treat and prevent PCP completely eliminate *Pneumocystis*, and prophylaxis is effective only while the selected medication is administered. Children with HIV who have experienced an episode of PCP should continue secondary PCP prophylaxis after completing treatment until CD4 counts exceed the threshold for initiating prophylaxis. The same criteria used for discontinuing primary prophylaxis apply **(strong, high).**[116]

Cases of PCP have been observed after secondary prophylaxis discontinuation in adults with HIV despite evidence of adequate immune reconstitution. Children who present with clinical signs and symptoms compatible with PCP after discontinuing prophylaxis should be evaluated thoroughly despite having normal or high CD4 counts or percentages **(strong, moderate).**[117] If PCP recurs at a CD4 count ≥200 cells/mm^3, lifelong prophylaxis should be considered. PCP prophylaxis is not to be discontinued in infants with HIV aged <1 year **(moderate, low).**

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	• TMP-SMX: 5–10 mg/kg/DAY (TMP-component) • Maximum individual dose: 160 mg/DOSE TMP-component. Several dosing regimens have been used successfully: o 3 days per week on consecutive or alternate days in divided doses every 12 hours o Daily as a single dose o Administration 2 days per week on consecutive or alternate days in doses divided every 12 hours has been used successfully in pediatric oncology patients.	Dapsone and atovaquone are both first-line alternatives (see text for relative risks and benefits), followed by aerosolized pentamidine as second line and IV pentamidine as third line. Dapsone • *Children Aged ≥1 Month:* 2 mg/kg/dose (maximum: 100 mg/dose) PO once daily or 4 mg/kg/dose (maximum 200 mg/dose) PO once weekly Atovaquone • *Children Aged 1–3 Months or >24 Months–12 Years:* 30–40 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged ≥13 Years:* 1,500 mg PO once daily Aerosolized Pentamidine Via Respirgard II Nebulizer *For Children Able to Comply With Its Use* • *Children Aged <5 Years:* Limited data regarding dosing. 9 mg/kg/dose or 150 mg/dose every month have been suggested. • *Children Aged ≥5 Years:* 300 mg every month IV Pentamidine • 4 mg/kg/dose every 3 to 4 weeks; maximum dose: 300mg/dose • Limited data regarding dosing frequency; based on use in oncology patients	Primary Prophylaxis Indicated for: • All infants with HIV or in whom HIV infection cannot be presumptively excluded beginning from age 4–6 weeks to 12 months, regardless of CD4 count or percentage • Children with stage 3 CD4 count: o *Children Aged 1 Year to <6 Years:* <500 cells/mm^3 or <22% o *Children Aged ≥6 Years:* <200 cells/mm^3 or <14% Criteria for Discontinuing Primary Prophylaxis • *Children Aged <1 Year:* Continue primary prophylaxis in children with HIV throughout the first year of life • Children Aged 1 year and older on ART for ≥6 months with CD4 count above age-specific stage 3 cutoff for >3 consecutive months: o *Children Aged 1 Year to <6 Years:* ≥500 cells/mm^3 *or* ≥22% o *Children Aged ≥6 Years:* ≥200 cells/mm^3 or ≥14% • Discontinuation can be considered in children ≥6 Years if on ART for ≥6 months with undetectable viral load and CD4 count 101–200 cells/mm^3 if intolerant of prophylaxis medications Criteria for Restarting Primary Prophylaxis • CD4 count below age-specific stage 3 cutoff

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Prophylaxis Prior PCP	Same as for primary prophylaxis.	Same as for primary prophylaxis.	Secondary Prophylaxis Indicated for: • Children with prior episode of PCP Criteria for Discontinuing Secondary Prophylaxis • Same as for primary prophylaxis Criteria for Restarting Secondary Prophylaxis • Same as for primary prophylaxis
Treatment	TMP-SMX 15–20 mg/kg/day (TMP-component) in divided doses every 6–8 hours IV or PO for 21 days (followed by secondary prophylaxis dosing)	If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy *Pentamidine* • 4 mg/kg/dose IV/IM once daily is the first-choice alternative regimen for severe disease. • Note: Close electrolyte and glucose monitoring required. Pentamidine can be changed to atovaquone after 7–10 days IV therapy. Atovaquone can be considered for initial therapy in mild-to-moderate disease. *Atovaquone* • Daily Dosing o *Children Aged 1–3 Months and >24 Months to 12 Years:* 30–40 mg/kg/dose PO once daily with food o *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food • Twice-Daily Dosing o *Children Aged ≥13 Years:* 750 mg/dose PO twice daily o Some experts use twice-daily dosing of atovaquone as alternative treatment for PCP in children aged <12 years.	After acute pneumonitis resolved in mild-to-moderate PCP, IV TMP-SMX can be transitioned to oral formulations. For oral administration, total daily dose of TMP-SMX can also be administered in three divided doses (every 8 hours). The following regimens have been used in adults, but data in children are limited: • Dapsone 2 mg/kg/dose PO once daily (maximum 100 mg/day) plus trimethoprim 5 mg/kg/dose PO every 8 hours • Primaquine base 0.3 mg/kg/dose PO once daily (maximum 30 mg/day) plus clindamycin 10mg/kg/dose IV or PO (maximum 600 mg/dose given IV and 300–450 mg/dose given orally) every 6 hours Chronic suppressive therapy (secondary prophylaxis) with TMP-SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis). Corticosteroids Adjunctive Therapy *Indication* • PaO_2 <70 mmHg at room air or alveolar-arterial oxygen gradient ≥35 mmHg

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
		▪ *Children Aged 1–3 Months and >24 Months to 12 Years*: 15–20 mg/kg/dose PO twice daily with food ▪ *Children Aged 4–24 Months:* 22.5 mg/kg/dose PO twice daily with food	*Prednisone Dose* • Days 1–5: 1 mg/kg/dose PO twice daily, then • Days 6–10: 0.5–1 mg/kg/dose PO twice daily, then • Days 11–21: 0.5 mg/kg/dose PO once daily. *Alternative Corticosteroid Regimens* • Adult Dosage of Prednisone: o Days 1–5: 40 mg/dose PO twice daily, then o Days 6–10: 40 mg/dose PO once daily, then o Days 11–21: 20 mg/dose PO once daily • Methylprednisolone IV: o Days 1–7: 1 mg/kg/dose every 6 hours, then o Days 8–9: 1 mg/kg/dose twice daily, then o Days 10–11: 0.5 mg/kg/dose twice daily, then o Days 12–16: 1 mg/kg/dose once daily

Note: Information included in these guidelines might not represent U.S. 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.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IM = intramuscular; IV = intravenous; PCP = *Pneumocystis* pneumonia; PO = oral; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

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Syphilis

(Last updated: October 6, 2013; last reviewed: January 24, 2022)

Panel's Recommendations

Congenital Syphilis

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

Sexually-Acquired Syphilis

Early Syphilis

- Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G for early-stage disease (i.e., primary, secondary, and early latent disease) (AII).
- HIV-infected children and adolescents with early syphilis (i.e., primary, secondary, early latent) should receive a single dose of benzathine penicillin G. Those with primary and secondary syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy, and those with early latent syphilis

should have clinical and serologic response monitored at 6, 12, 18, and 24 months after therapy (AIII) (For comprehensive discussion and recommendations, see the Centers for Disease Control and Prevention STD Treatment Guidelines, 2010).

- Re-treatment of patients with early-stage syphilis (i.e., primary, secondary, early latent) and evaluation for HIV infection is recommended for those who:
    - Do not experience at least a fourfold decrease in serum nontreponemal test titers 6 to 12 months after therapy,
    - Have a sustained fourfold increase in serum nontreponemal test titers after an initial reduction post-treatment, or
    - Have persistent or recurring clinical signs or symptoms of disease.
- Individuals whose titers do not decline should at a minimum receive additional clinical and serologic follow-up. If such additional follow-up cannot be ensured, re-treatment is recommended. Because occult central nervous system infection may be signaled by persistently elevated serum nontreponemal test titers, evaluation of CSF can be considered in the event of such persistently elevated titers (BIII).
- If initial CSF examination demonstrates pleocytosis, repeat lumbar puncture should be conducted, and then every 6 months until the cell count is normal (AIII).

Late Latent Syphilis

- For late latent disease, 3 doses of benzathine penicillin G should be administered over 3 weeks (AIII).
- Patients with late-latent syphilis should have CSF examination if they have clinical signs or symptoms attributable to syphilis, a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (i.e., less than fourfold decline in nontreponemal test titer) within 12 to 24 months after therapy if initial titer was high (>1:32) (BIII). CSF examination should also be performed. Treatment for neurosyphilis should be initiated if CSF examination is positive for neurosyphilis.
- Benzathine penicillin G should be administered at 1-week intervals for 3 weeks to patients in whom CSF examination does not confirm the diagnosis of neurosyphilis (AIII).

Neurosyphilis

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

For All Syphilis

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

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

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or

observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies **in children**† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies **in adults** with long-term clinical outcomes with accompanying data **in children**† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

†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: • N/A Criteria for Discontinuing Primary Prophylaxis: • N/A Criteria for Restarting Primary Prophylaxis: • N/A
Secondary Prophylaxis	N/A	N/A	Secondary Prophylaxis Indicated: • N/A Criteria For Discontinuing Secondary Prophylaxis: • N/A Criteria For Restarting Secondary Prophylaxis: • N/A
Treatment	Congenital *Proven or Highly Probable Disease*: • Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 12 hours for the first 7 days of life, and then every 8 hours for 10 days • 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 *Possible Disease*: • Treatment options are influenced by several factors, including maternal treatment, titer, and response to therapy; and infant physical exam, titer,	Congenital *Proven or Highly Probable Disease (Less Desirable if CNS Involvement):* • Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days *Possible Disease*: • 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. 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. In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable. 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. Acquired *Early Stage (Primary, Secondary, Early Latent)*: • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM for 1 dose *Late Latent* • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM once weekly for 3 doses *Neurosyphilis (Including Ocular)*: • 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

Updated: December 22, 2025
Reviewed: December 22, 2025

Panel's Recommendations

Preventing Exposure

- Children with HIV should avoid ingesting undercooked meals that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts (AIII).

Primary Prophylaxis

- Prophylaxis against *Toxoplasma* encephalitis (TE) should be administered to children with HIV who are *Toxoplasma*-seropositive and aged <1 year with CD4 T lymphocyte (CD4) cell percentage ≤26% (CD4 count ≤750 cells/mm^3), aged 1–5 years with CD4 percentage ≤22% (CD4 count ≤500 cells/mm^3), or ≥6 years with CD4 count ≤100 cells/mm^3 (AIII).
- The preferred agent for TE prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMX) which is administered by weight-equivalent dosing for children (AII*). One double-strength tablet of TMP-SMX, three times weekly (or 3 consecutive days a week), is an alternative (AII*). Alternative therapies, such as dapsone/pyrimethamine plus leucovorin (BI*) or atovaquone with or without pyrimethamine (CIII), exist for those who do not tolerate TMP-SMX.
- Preventive therapy can be discontinued once a child responds to antiretroviral therapy (ART) with a sustained rise (>3 months) in children aged 1–5 years with CD4 percentage >22% (CD4 count >500 cells/mm^3) or children aged ≥6 years with CD4 count >200 cells/mm^3 (see Introduction, Table 2) (AIII). Prophylaxis should not be discontinued in patients less than 1 year of age. Primary prophylaxis should be reintroduced if these parameters are not met (BIII).

Treatment

- Most experts recommend treatment with acute toxoplasmosis during pregnancy in an attempt to prevent fetal infection. For more extensive information on diagnosis, prevention, and treatment during pregnancy with toxoplasmosis, please see the Toxoplasmosis section of the Adult and Adolescent Opportunistic Infection Guidelines.
- Empiric therapy should be strongly considered for newborns of mothers with HIV 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 plus sulfadiazine, with supplementary leucovorin (folinic acid) (AII).
- The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin (AI*).
- The recommended treatment duration for congenital toxoplasmosis in infants with HIV is 12 months (AIII).
- Therapy for acquired toxoplasmosis in children with HIV is pyrimethamine plus sulfadiazine and leucovorin (AII). Older children with HIV and acquired central nervous system, 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.
- Anticonvulsants should be given to children with TE who have a history of seizures but should not be administered prophylactically to children without a history of seizures (AIII).
- Corticosteroids are recommended for children with HIV and central nervous system toxoplasmosis when cerebrospinal fluid protein is highly elevated (i.e., >1,000 mg/dL) or when focal lesions with substantial mass effect are present (BIII).

Panel's Recommendations
Secondary Prophylaxis • Children who have completed initial therapy for TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) unless ART results in immune reconstitution (AI*). The preferred suppressive therapy for TE is sulfadiazine plus pyrimethamine and leucovorin (AI*). • Secondary prophylaxis can be discontinued in children on ART aged >1 year who are asymptomatic after completing TE therapy, with a concomitant and sustained rise (>3 months) to CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1–5 years or CD4 >200 cells/mm^3 in children ≥6 years of age (AIII). Secondary prophylaxis should be reinstituted if these parameters are not met (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 postpubertal 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 mothers who sustain primary *Toxoplasma* infection during pregnancy. While *Toxoplasma* infection is typically asymptomatic in immunocompetent hosts, severe disease can occur in immunocompromised hosts or congenital infection. Comprehensive guidelines for the diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States were published in 2017.[1] The estimated incidence of congenital toxoplasmosis in the United States is 1 case per 1,000 to 12,000 live-born infants.[2-4] In people born in the United States who are aged 12–49 years, the age-adjusted *T. gondii* seroprevalence decreased from 14.1% (95% confidence limit [CL] 12.7% to 15.5%) in NHANES III (1988–1994) to 9.0% (95% CL 7.6%, 10.5%) in NHANES 1999–2004 to 6.7% (95% CL 5.3%, 8.2%) in NHANES 2009–2010 ($P < 0.001$ linear trend).[5] 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.[6] In the United States, eating raw shellfish including oysters, clams, and mussels was identified as a novel risk factor for acute infection.[7] 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.[8] Indeed, *Toxoplasma* infection in humans in the United States has declined despite increased cat ownership.[6] While the risk of toxoplasmosis transmission from indoor cats to humans is generally lower compared to outdoor cats who are exposed to mice and other rodents, it is still important for cat owners to take precautions to minimize the risk of exposure. Such precautions include keeping cats indoors, feeding cats commercial cat food rather than raw meat, providing a clean litter box, and promptly removing feces.[9,10]

The overall risk of perinatal transmission in women without HIV who acquire primary *Toxoplasma* infection during pregnancy is 29% (95% confidence interval, 25% to 33%), with variation depending

upon the trimester during which primary maternal infection occurs.[11] The risk of congenital infection is low among infants born to women who become infected during the first trimester (2% to 6%) but increases sharply thereafter, with a risk as high as 81% in women who become infected during the last few weeks of pregnancy.[11,12] Infection of the fetus in early gestation usually results in more severe disease than does infection late in gestation.[13]

The prevalence of latent *Toxoplasma* infection among women with and without HIV in the United States was assessed in a cross-sectional study of 2,525 nonpregnant women enrolled in the Women's Interagency Health Study.[14] The overall prevalence of *Toxoplasma* seropositivity was 15% and did not differ by HIV status, but a prevalence of 41% was seen among women born outside of the United States. Similarly in another study, age-adjusted seroprevalence among women of childbearing age (15–44 years) has declined over time (15%, 11%, 9%, and 7.5% in 1988–1994, 1999–2000, 2009–2010, 2011–2014, respectively) suggesting that 92.5% of women of childbearing age are susceptible to infection.[1] However, the number of toxoplasmosis deaths in people with HIV declined from 2000 to 2010.[1,15] The overall rate of perinatal transmission of *Toxoplasma* in pregnant women with HIV is unknown; however, a few cases of perinatal transmission of *Toxoplasma* in women with HIV have been reported.[16-20] People with HIV may be at increased risk of perinatal *T. gondii* transmission, and serologic testing for *Toxoplasma* should be performed in the setting of pregnancy with HIV. Perinatal transmission of *T. gondii* is rare from women without HIV who acquired *Toxoplasma* infection before pregnancy.[21] However, in people with HIV coinfection, perinatal transmission has been observed with chronic *Toxoplasma* infection (transmission rate: <4%), presumably due to reactivation of *Toxoplasma* organism replication in those who are severely immunosuppressed.[16-19] There is a higher rate of congenital toxoplasmosis when the mother has active clinical toxoplasmosis during gestation.[22] Central nervous system (CNS) infection with *T. gondii* was reported as an AIDS-indicating condition in fewer than 1% of pediatric AIDS cases before the advent of antiretroviral therapy (ART).[23] Since the advent of ART, this condition is rarely encountered in children with HIV in the United States. CNS toxoplasmosis occurred in 5 of 2,767 (0.2%) children with HIV who were enrolled in the long-term follow-up study Pediatric AIDS Clinical Trials Group 219c in the ART era.[24] *Toxoplasma* infection is considered to have occurred *in utero* in most cases of *Toxoplasma* encephalitis (TE) observed in children with HIV. More rarely, TE has been reported in older children with HIV, who presumably had primary acquired toxoplasmosis.[25,26] 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% to 90%) are asymptomatic at birth.[27] However, most asymptomatic children (50% to 75%) will go on to develop late sequelae such as retinitis, visual impairment, and intellectual or neurologic impairment, with onset of symptoms occurring several months to years after birth. Symptoms in newborns may present as either generalized disease or predominantly neurologic disease, including symptoms such as maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly, jaundice, hematologic abnormalities (e.g., anemia, thrombocytopenia, neutropenia), and substantial CNS disease, including hydrocephalus, diffuse intracerebral calcification, microcephaly, chorioretinitis, and seizures. Cerebrospinal fluid (CSF) protein may be mild to moderately elevated and may have mononuclear CSF pleocytosis, and these nonspecific findings should raise suspicion for CNS toxoplasmosis[28]

Toxoplasmosis acquired after birth in immunocompetent patients is most often initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly.[29]

TE should be considered in all children with HIV with new neurologic findings, but especially among those with severe immunosuppression.[27] 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 with clinical exam and neuroimaging and lumbar puncture is indicated for children with in whom toxoplasma chorioretinitis is diagnosed. Lumbar puncture is not recommended for adolescents with toxoplasma chorioretinitis who are not immunosuppressed. Ocular toxoplasmosis appears as white retinal lesions with little associated hemorrhage; visual loss can occur initially.[30]

Less frequent presentations in children with HIV with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis.[19,31]

Diagnosis

All infants born to mothers who have HIV and are seropositive for *Toxoplasma* are at risk for congenital toxoplasmosis.[32] Infants born to mothers from an area where *Toxoplasma* is endemic may be at a higher risk of congenital toxoplasmosis. Congenital toxoplasmosis can be diagnosed by enzyme-linked immunoassay or an immunosorbent assay to detect *Toxoplasma*-specific immunoglobulin M (IgM), immunoglobulin A (IgA), or immunoglobulin E (IgE) in neonatal serum within the first 6 months of life, or persistence of specific immunoglobulin G (IgG) antibody beyond age 12 months.[33-37] IgA may be more sensitive for detecting congenital infection than IgM or IgE.[34] However, approximately 20% to 30% of infants with congenital toxoplasmosis will not be identified during the neonatal period with IgA or IgM assays.[35]

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.[34]

Additional diagnostic methods for *Toxoplasma* infection in newborns include isolating the *Toxoplasma* parasite by mouse inoculation or inoculation in tissue cultures of 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, urine, vitreous fluid, bronchoalveolar lavage fluid, cord blood) in a reference laboratory.[34,35] *Toxoplasma* PCR assay sensitivity varies widely (15% to 85% for blood) and specificity appears to be high (>95%). Overall sensitivity is approximately 90% in amniocentesis performed in pregnant women >18 weeks of gestation and at least 4 weeks after maternal infection. In the CSF, PCR sensitivity also varied widely in studies. In, immunocompromised patients, PCR sensitivity had a sensitivity of 87% when done in the first 7 days of treatment; Studies in immunocompetent patient have shown between 69% to 100% sensitivity in patients tested early as well.[38-41] 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 computer tomography [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.[42] TE has been rarely reported in individuals without *Toxoplasma*-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis, particularly in individuals with profound immunosuppression. Brain 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. MRI is more sensitive and will confirm basal ganglia lesions in most people.[43] 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 brain tissue is often required for diagnosis. Definitive TE diagnosis 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 individuals who do not respond to specific therapy.

Prevention Recommendations

Preventing Exposure

All children and adolescents with HIV and their caregivers should be counseled about sources of *T. gondii* infection such as raw or undercooked meat, including lamb, beef, pork, or venison. A recent case-control study also showed risk associated with eating raw oysters, clams, or mussels.[7]

According to U.S. Department of Agriculture guidelines, all whole-cut meat excluding poultry (e.g., lamb, beef, and pork) should be cooked to an internal temperature of 145°F (63°C) with a food thermometer placed in the thickest part of the meat, then the meat should be allowed to rest for 3 minutes during which time it will maintain the attained temperature. Ground meat, excluding poultry, should be cooked to at least 160°F (71°C) but do not require a rest time. All poultry should be cooked to at least 165°F (74°C). Because one study has found that *T. gondii* can survive at 147.2°F (64°C) for 3 minutes, higher temperatures should be considered for those who are immunosuppressed.[44]

Handwashing should occur 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. Untreated drinking water should not be consumed. Stray cats should not be handled or adopted; a cat already in the household should be kept inside and the litter box should be changed daily, preferably by an individual without HIV who is not pregnant. Cats should only be fed canned or dried commercial food, or well-cooked table food; raw or undercooked meats should be avoided. Children and adolescents with HIV do not need to part with their cats or to have their cats tested for toxoplasmosis but should avoid contact with contaminated cat feces or soil containing contaminated cat feces. Outdoor sandboxes should be covered to avoid accidental contamination and contact with cat feces. Ingestion of undercooked meats that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts should be avoided **(AIII).**

Preventing Disease

In the United States, routine *Toxoplasma* serologic screening is not recommended for children with HIV whose mother does not have toxoplasmosis because of its low incidence. Adolescents with HIV who have no history of previous *Toxoplasma* infection should undergo serologic testing. 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 children with HIV aged >12 months. In addition, serologic testing for *Toxoplasma* should be done during pregnancy with HIV.

There is a lack of good quality data in randomized placebo-controlled trials in adults and children to show a benefit from toxoplasmosis prophylaxis, although these trials may have been underpowered to detect differences.[45,46] Given that many of these trials were done prior to the advent of combination ART, the benefit of prophylaxis is likely less while on ART. Data from an observational retrospective study are used to support the recommendation that *Toxoplasma*-seropositive adolescents and adults who have CD4 counts <100 cells/mm^3 should be given prophylaxis against TE.[47] Specific levels of immunosuppression that increase the risk of TE in children are less well defined. However, adult data suggest that increased risk for developing TE in children may be extrapolated to age-appropriate CD4 parameters corresponding to advanced immunosuppression.[45,48,49]

In children with HIV, such parameters are based on age-specific CD4 count or CD4 percentage of total lymphocytes (see Introduction, Table 2). *Toxoplasma*-seropositive children with HIV aged <1 year with CD4 percentage ≤26% (CD4 count ≤750 cells/mm^3), aged 1 to 5 years with CD4 percentage ≤22% (CD4 count ≤500 cells/mm^3), or aged ≥6 years with CD4 count ≤100 cells/mm^3 should be administered prophylaxis against TE **(AIII).**

Toxoplasma-seronegative adults and adolescents with HIV 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 counts decline to ≤100 cells/mm^3 to determine whether they have seroconverted to *Toxoplasma.* In adolescents and adults with HIV, the preferred regimen for PCP prophylaxis is one double-strength trimethoprim-sulfamethoxazole (TMP-SMX) tablet daily because of its high efficacy, relative safety, low cost, broad antimicrobial spectrum, and concurrent efficacy as TE prophylaxis.[47] Data from trials in adults support once-daily TMP-SMX as the preferred regimen in children using weight-equivalent dosing (See Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis) **(AII*).** One double-strength tablet of TMP-SMX, three times weekly (or 3 consecutive days a week), is an alternative **(AII*).**[50] Other alternative dosing schedules include TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth every day or TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth three times weekly on alternate days. Based on data from systematic reviews and adult randomized controlled trials, dapsone-pyrimethamine plus leucovorin—which is also effective against PCP—is the recommended alternative for people who cannot tolerate TMP-SMX **(BI*).**[51-54] Screening for glucose-6-phosphate dehydrogenase deficiency should be done before initiating dapsone.

Atovaquone with or without pyrimethamine also can be considered for those who cannot tolerate TMP-SMX **(CIII).** Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin is not recommended. Aerosolized pentamidine does not protect against TE and also is not recommended.[47,55] Severely immunosuppressed children who are seropositive for *Toxoplasma* and

who are not receiving TMP-SMX or atovaquone should be given prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine).

Discontinuing Primary Prophylaxis

Primary prophylaxis can be discontinued once a child responds to ART with a sustained rise (>3 months) in CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1 to 5 years, or CD4 count >200 cells/mm^3 for children aged ≥6 years **(AIII).**

Multiple observational studies[49,56,57] and two randomized trials[58,59] have reported that primary prophylaxis can be discontinued with minimal risk of TE in people who have responded to ART with an increase in CD4 count to ≥200 cells/mm^3 for ≥3 months. Although people with CD4 counts of <100 cells/mm^3 are at greatest risk of TE, the risk of TE when CD4 counts increase to between 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 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 children with HIV whose immunologic status improves on ART. Therefore, based on adult data, discontinuation of TMP-SMX may be safe once a child responds to ART with a sustained rise in CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1 to 5 years, and CD4 count >200 cells/mm^3 in children aged at least 6 years **(AIII).** Prophylaxis should not be stopped in children aged less than 1 year. A sustained response in children has been defined as a CD4 count or percentage above the threshold level for >3 consecutive months. It should be noted that older literature may not align with new cut-off points for immunosuppression in the revised surveillance case definition for HIV.

Prophylaxis should be reintroduced children ≥6 years old with HIV **(BIII)** if the CD4 count decreases to ≤200 cells/mm^3. For children with HIV aged <6 years prophylaxis should be reintroduced, if the CD4 percentage falls below 22% (CD4 count ≤500 cells/mm^3) in children aged 1 to 5 years, and if the CD4 percentage falls below 26% (CD4 count ≤750 cells/mm^3) in children aged less than 1 year (**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 infectious disease specialist with expertise in managing toxoplasmosis. Although controversy exists about the efficacy of treating pregnant women who have acute toxoplasmosis in an attempt to prevent perinatal transmission,[60] most experts would recommend such therapy.[32]

For more extensive information on the diagnosis, prevention, and treatment during pregnancy with toxoplasmosis, please see the Toxoplasmosis section of the Adult and Adolescent Opportunistic Infection Guidelines.

Given that a delay in initiation of therapy was associated with poor neurologic outcomes, empiric therapy should be strongly considered for newborns of mothers with HIV who had symptomatic or

asymptomatic primary *Toxoplasma* infection during pregnancy, regardless of whether treatment was administered during pregnancy **(BIII).**[28]

These treatment recommendations for children with HIV are based on studies of children with congenital toxoplasmosis without HIV. A systematic review of cohort studies based on universal screening for congenital toxoplasmosis did not show a reduced risk of congenital manifestations with treatment during pregnancy.[60]

The preferred treatment for congenital toxoplasmosis and acquired toxoplasmosis in children with HIV is similar. For these scenarios, the preferred treatment is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII).**[28,30,61-63] Although the optimal duration of therapy is undefined, the recommended duration of treatment for congenital toxoplasmosis in infants without HIV is 12 months **(AIII).**[30] Older children with HIV and acquired CNS, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(AI*).** Acute therapy should be continued for at least 6 weeks, assuming clinical and radiologic improvement **(BII*).**[64]

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*).** As an alternative to clindamycin, azithromycin has also been used with pyrimethamine and leucovorin in sulfa-allergic adults, but this regimen has not been studied in children.[65] Extrapolation of azithromycin 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. 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 randomized trial in 77 adults, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.[66] Others have reported similar efficacy in open-label observational studies.[67,68] 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.[69] However, these data have not been duplicated in people with HIV; therefore, this regimen cannot be recommended for this group of patients.

Based upon treatment of congenital toxoplasmosis in children without HIV, corticosteroids such as dexamethasone and prednisone may be beneficial in certain scenarios and are recommended for all children with HIV and CNS disease when CSF protein is highly elevated (i.e., >1,000 mg/dL) or when there is vision-threatening chorioretinitis with macular involvement or 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 but should not be administered prophylactically to children without a history of seizures **(AIII).** Anticonvulsants, if administered, should be continued at least through acute therapy for CNS toxoplasmosis.

Although the initiation of ART assists in treating many opportunistic infections and malignancies, it has not been definitively shown to improve the outcome of TE therapy. In line with adult treatment practices, many physicians would initiate ART within 2 to 3 weeks of a toxoplasmosis diagnosis, based on research demonstrating that early ART initiation significantly reduces the risk of AIDS or death in people with opportunistic infections (except tuberculosis) compared to deferred treatment.[70]

Monitoring Response to Therapy and Adverse Events, Including IRIS

Children with TE should be routinely monitored for clinical and radiologic improvement and 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 adults with HIV and has not been described in children with HIV, although it could presumably occur.[71,72] In pregnant women with HIV, IRIS may pose additional risk to the fetus,[73] although no unique risk for pregnant women coinfected with HIV and *Toxoplasma* has 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. 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 for 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, diarrhea, pseudomembranous colitis) and hepatotoxicity.

TMP-SMX therapy may cause rash, pruritus, GI symptoms (nausea, vomiting, anorexia), pseudoelevations in blood urea nitrogen and serum creatinine (without changes in estimated glomerular filtration rate), photosensitivity, hyperkalemia (higher doses, chronic renal insufficiency, or with concomitant potassium sparing medications), or blood dyscrasias (e.g., anemia, neutropenia, and thrombocytopenia).[74] Atovaquone has been associated with GI symptoms (diarrhea, nausea, vomiting abdominal pain, diarrhea), rash, headache, fever, and insomnia.[75]

Drug interactions between anticonvulsants and antiretroviral drugs should be evaluated. Patients receiving corticosteroids should be closely monitored for the 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 may be considered.

Preventing Recurrence

People who have completed initial therapy for acquired TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) [61,62] until immune reconstitution occurs with ART. The combination of sulfadiazine plus pyrimethamine and leucovorin is strongly recommended for TE chronic maintenance therapy **(AI*).** Pyrimethamine plus clindamycin with leucovorin is recommended as an alternative to sulfadiazine plus pyrimethamine and leucovorin in people who cannot tolerate sulfa drugs **(BI*);** however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well. Data on adults indicate atovaquone with or without pyrimethamine can also be considered for children **(CIII).** Limited data support the use of TMP-SMX for secondary prophylaxis;[76] this regimen should be used only for people who cannot tolerate pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CIII).**

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 count of >200 cells/mm^3 after ART (i.e., >6 months).[49,57,59,77,78] Discontinuing chronic maintenance therapy in adolescents and adults with HIV 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 ART in children has not been studied extensively. However, given the data in adults, for children with HIV older than 1 year with history of TE, consider discontinuing secondary prophylaxis against *T. gondii* after they have completed TE therapy and are asymptomatic, and once the CD4 percentage has risen to >200 cells/mm^3 in those ≥6 years old and the CD4 percentage is >22% (CD4 count >500 cells/mm^3) in those aged 1 to 5 years for >3 consecutive months **(AIII).** Prophylaxis should be reinstituted if these parameters are not met. Children with HIV with congenital toxoplasmosis should receive 12 months of initial therapy for TE; therefore, secondary prophylaxis would not be appropriate in the first year of life.

Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	TMP-SMX 150/750 mg/m^2 body surface area once daily PO	**For Children Aged ≥1 Month:** • Dapsone 2 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO every 3 days (continued for 1 week after pyrimethamine completed due to long half-life) For Children Aged 1–3 Months and >24 Months: • Atovaquone 30 mg/kg body weight (maximum 1,500 mg) PO once daily with food For Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *with or without* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* leucovorin 5 mg PO every 3 days Acceptable Alternative Dosage Schedules for TMP-SMX • TMP-SMX 150/750 mg/m^2 body surface area per dose PO three times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily PO every day • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily PO three times weekly on alternate days	Primary Prophylaxis Indicated for: *Children With IgG Antibody to Toxoplasma and Severe Immunosuppression Who Are:* • Aged <1 year with CD4% ≤26% or CD4 ≤750 cells/mm^3, *or* • Aged 1–5 years with CD4% ≤22% or CD4 ≤500 cells/mm^3, *or* • Aged ≥6 years with CD4 count ≤100 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis Note: Do not discontinue in children aged <1 year. • Aged 1–5 years with CD4 count >500 cells/mm^3 for >3 consecutive months *or* • Aged ≥6 years with CD4 count >200 cells/mm^3 for >3 consecutive months Criteria for Restarting Primary Prophylaxis: • Aged 1–5 years with CD4 count <500 cells/mm^3 *or* • Aged ≥6 years with CD4 count <200 cells/mm^3

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Prophylaxis (Suppressive Therapy)	• Sulfadiazine 85–120 mg/kg body weight per day in 2–4 divided doses (maximum 2–4 g per day) PO, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days	• Clindamycin 7–10 mg/kg body weight per dose (max 600 mg/dose) PO three times daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days Children Aged 1–3 Months and >24 Months • Atovaquone 30 mg/kg body weight PO (maximum 1,500 mg) once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 body surface area PO once daily Children Aged 4–24 Months *Option 1* • Atovaquone 45 mg/kg body weight PO once daily with food, *with or without* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* leucovorin (when using pyrimethamine), 5 mg PO every 3 days *Option 2* • Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 body surface area PO once daily	Secondary Prophylaxis Indicated • Prior TE Note: Limited data in children is available for alternative regimens. TMP-SMX only to be used if individual is intolerant to other regimens. Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria are Fulfilled*: • Completed initial therapy for TE, *and* • Asymptomatic for TE, *and* • Aged ≥6 years old with CD4 >200 cells/mm^3 in those or CD4% >22% (CD4 count >500 cells/mm^3) in those aged 1–5 years for 3 consecutive months Criteria For Restarting Secondary Prophylaxis: • CD4 count ≤200 cells/mm^3 and CD4% ≤22% (CD4 count ≤500 cells/mm^3) in those aged 1–5 years 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.

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Congenital Toxoplasmosis • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 mg PO or IM three times weekly, *plus* • Sulfadiazine 50 mg/kg body weight PO twice daily *Treatment Duration* • 12 months Acquired Toxoplasmosis *Acute Induction Therapy (Followed by Chronic Suppressive Therapy)* • Pyrimethamine loading dose of 1 mg/kg body weight (maximum 50 mg) PO twice daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) PO once daily, *plus*	For Sulfonamide-Intolerant Patients: • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 PO or IM three times weekly, *plus* • Clindamycin 5–7.5 mg/kg body weight PO or IV (maximum 600 mg/dose) per dose four times daily	Congenital Toxoplasmosis • For infants born mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of treatment during pregnancy. Acquired Toxoplasmosis • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less-than-daily dosing. • The following regimens are used in adults but have not been studied in children: o TMP-SMX 5/25 mg/kg body weight per dose IV or PO given twice daily as an alternative to pyrimethamine-sulfadiazine o Atovaquone 1,500 PO twice daily administered: ▪ with pyrimethamine and leucovorin, *or* ▪ with sulfadiazine, *or* ▪ alone, for those with pyrimethamine and sulfadiazine intolerance o Azithromycin 900–1,200 mg daily (corresponding to 20 mg/kg daily, maximum 1,000 mg in children) administered with pyrimethamine-leucovorin • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or when focal lesions with significant mass effects are present, with discontinuation as soon as clinically feasible.

Indication	First Choice	Alternative	Comments/Special Issues
	• Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) PO per dose four times daily, *plus* • Leucovorin 10–20 mg PO once daily, continued for one week after stopping pyrimethamine *Treatment Duration (Followed by Chronic Suppressive Therapy)*: • ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)		• Anticonvulsants should be administered to people with a history of seizures and continued through the acute treatment but should not be used prophylactically. • Sulfadiazine may be given as 2 to 4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight. • Consider screening for G6PD deficiency before starting sulfadiazine or TMP-SMX in people from regions with high prevalence of severe G6PD deficiency.

Key: CBC = complete blood count; CD4 = CD4 T lymphocyte; CD4% = CD4 T lymphocyte percentage; CNS = central nervous system; CSF = cerebrospinal fluid; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; IM = intramuscular; IV = intravenous; PO = orally; TE = Toxoplasma encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole

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Varicella-Zoster Virus Disease

Updated: April 23, 2026
Reviewed: April 23, 2026

Panel's Recommendations
Vaccination and Post-exposure Prophylaxis • Children aged ≥12 months and adolescents with HIV stage 1 or 2 without evidence of immunity to varicella should receive two doses of single-antigen varicella vaccine (VAR; Varivax) according to routine or catch-up vaccination schedules (AI). VAR is not recommended for children with HIV stage 3 (AIII). • Children and adolescents with HIV who are susceptible to varicella or who have severe (stage 3) immunosuppression and have had a significant exposure to varicella or herpes zoster (HZ) should receive varicella-zoster immune globulin (available as intramuscular VariZig) as soon as possible (ideally within 96 hours but up to 10 days) after exposure (AI). Varicella vaccine should be administered 5 months after receipt of VariZig in eligible children (AIII). • Refer to the Varicella Vaccine section of Figure 1. Recommended Immunization Schedule for detailed recommendations. Treatment of Varicella and Herpes Zoster • Intravenous (IV) acyclovir is the preferred drug for the initial treatment of varicella infection in children with HIV, especially those with severe immunosuppression (stage 3) or those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions (AI). IV acyclovir should be initiated as soon as possible after varicella lesions appear and shows the most benefit when initiated within 24 hours of rash onset. For children with HIV stage 1 or 2 who have mild varicella disease, varicella can be initially treated with oral valacyclovir (if ≥3 months of age) or oral acyclovir (BII). • For children ≥3 months of age with HIV and uncomplicated HZ, oral valacyclovir is the treatment of choice (AI*). Initial IV acyclovir administration is recommended for children with HIV with severe immunosuppression (stage 3) and HZ, extensive multidermatomal HZ, trigeminal or sacral nerve involvement, disseminated infection, visceral involvement, or otherwise complicated HZ (AI*). • Children in whom lesions continue to develop, fail to heal, or progress after 7 days of treatment may have acyclovir-resistant varicella-zoster virus. Resistance is rare and primarily occurs in immunocompromised individuals. Because resistance testing may be difficult to arrange and delays treatment, the decision to change therapy should be based on current clinical status, and foscarnet should be administered immediately if clinical status is deteriorating (AII*).
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 postpubertal adolescents.*

Epidemiology

Varicella-zoster virus (VZV) is the infectious agent responsible for chickenpox (varicella) and shingles (herpes zoster [HZ]). Before the implementation of universal immunization in the United States in 1995, approximately 4 million cases of varicella occurred annually. After initiation of universal immunization, disease has since declined overall by >97%. The most impressive declines

(99%) were seen among persons aged <20 years who were born after vaccine introduction and in whom severe disease has mostly been eliminated.[1] Another unanticipated benefit of the vaccination program is the reduction in risk of HZ in both healthy and immunocompromised children. In healthy children, vaccination is associated with an approximately 80% lower risk compared with unvaccinated children).[2]

VZV is highly contagious and can be transmitted either via direct contact with VZV lesions (from varicella or HZ) or through airborne particles.[3] Clinical infection develops in about 80% (range: 61–100%) of susceptible individuals exposed to VZV within a household, and health care–associated transmission is well documented.[4] Notably, varicella is more contagious than HZ.[5] The virus is extremely labile, unable to survive for long in the environment, and, therefore, is not transmitted through fomites.

After initial infection or vaccination with VZV, VZV establishes latency in sensory (dorsal root, cranial nerve, and autonomic) ganglia, where its reactivation results in HZ. Once established, VZV latency persists for life, and reactivation causing HZ occurs in approximately 30% of people with varicella. Although HZ is less contagious than varicella, VZV can still spread from HZ lesions through direct contact or via airborne particles, causing varicella infection in unvaccinated people who have never had varicella. HZ occurs when VZV-specific cellular immunity, first stimulated by primary infection, declines with age. In addition, VZV-specific cellular immunity may be depressed by HIV infection, with evidence suggesting that children with HIV have difficulty maintaining anti-VZV immunoglobulin G (IgG) levels due to failure of reactivating memory responses.[6-9] Although the incidence of HZ has declined significantly in children with HIV since the advent of antiretroviral therapy (ART), the incidence remains at 1 to 3 cases per 100 patient-years, approximately 10 to 25 times higher than in the general population.[10-15] Risk factors for the development of HZ include low incident (i.e., coincidental with HZ reactivation) or nadir CD4 T lymphocyte (CD4) cell count/percentage, high HIV RNA plasma viral load (e.g., >10,000 copies/mL), and acquisition of varicella when the CD4 percentage is <15%.[11,16,17] As in adults, the frequency of HZ recurrences in children correlates inversely with the CD4 count.[11,18]

Immunocompromised people with primary or reactivated VZV infection are at increased risk of serious disease. Severe varicella and disseminated HZ more commonly develop in children with HIV stage 3—or congenital T lymphocyte defects—than in people with B lymphocyte abnormalities. Other groups at higher risk of severe or complicated varicella include infants, adolescents, children with chronic cutaneous or pulmonary disorders, and those receiving systemic corticosteroids, other immunosuppressive therapy, or long-term salicylate therapy.

Clinical Manifestations

Primary infection with VZV results in varicella, which is a generalized, pruritic, erythematous vesicular rash often accompanied by fever and other systemic symptoms. In unvaccinated individuals, the rash typically consists of hundreds of lesions in various stages of development (e.g., papules, vesicles). Crusted lesions are indicative of healing. Breakthrough cases may occur in vaccinated children, but the rash and other symptoms are usually milder. The incubation period for varicella ranges from 10 to 21 days (average of 14 days) in immunocompetent children. A brief prodrome of malaise and fever may occur, followed by the appearance of skin lesions, which occur more frequently on the face and trunk than on the extremities.

Varicella causes more morbidity in individuals with HIV than in the general population. Initial reports of varicella in children with untreated HIV described severe disease manifestations and chronic, atypical skin lesions, including nonhealing ulcers that become necrotic, crusted, and hyperkeratotic.[19,20] Clinically important systemic involvement, especially in severely immunocompromised children, can include neurologic manifestations (e.g., encephalitis, cerebellar ataxia, transverse myelitis), hepatitis, rapidly progressive pneumonitis, and multiorgan failure with intravascular coagulation.[21] Subsequent studies suggest less complicated varicella infections in children with HIV who are receiving ART or who have higher CD4 counts at the time of infection.[16,22] However, active infection may last longer than normal, with new lesions and fever developing into the second week of illness. In addition, the rate of complications is higher in children with HIV than in otherwise healthy children with varicella.[23]

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.[20,24] The lesions are characteristically varicelliform at onset but evolve into nonhealing ulcers or necrotic, crusted, and hyperkeratotic verrucous lesions. Chronic VZV was reported in 14% of children with HIV who had VZV in the pre-ART era, usually in children with low CD4 counts.[18]

Congenital varicella syndrome (CVS), which can occur when VZV crosses the placenta and is transmitted to the fetus, is characterized by multi-system anomalies. The estimated incidence of CVS is 0.59% and 0.84% for women infected with VZV during the entire pregnancy and for those infected during the first 20 weeks of pregnancy, respectively.[25] CVS only occurs in infants born to women with primary varicella infection and does not occur in infants born to women with HZ during pregnancy.

Perinatal VZV transmission can also occur 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%.[26,27] In comparison, in infants born to mothers who developed varicella ≥5 days before delivery, long enough to allow the transfer of VZV antibodies across the placenta, perinatal varicella can still occur but is typically less severe and with an extremely low mortality rate.

HZ classically presents as a painful or pruritic, vesicular, dermatomal rash. Typically, pain precedes the rash by 2 to 3 days. Less typical rashes—including rashes that extend beyond dermatomal boundaries, are bilaterally distributed, or that are generalized—can occur in children with HIV. Multiple recurrent episodes of HZ can also be seen.[11,18] Disseminated HZ with multiorgan involvement can occur, with or without the typical rash. Encephalitis long after HZ, or without rash, has been reported in children with HIV.[28] Given similarities between the characteristic rash of HZ and herpes simplex virus (HSV), polymerase chain reaction (PCR) testing of vesicular fluid is necessary to rule out HSV for diagnosis and treatment.

Retinitis, a potential complication of VZV infection in children and adolescents with HIV,[29,30] may be confused with cytomegalovirus (CMV) retinitis.[31] Acute retinal necrosis can be a complication of VZV infection in children with HIV regardless of CD4 count. Progressive outer retinal necrosis, often associated with HZ, typically occurs in individuals with CD4 counts <50 cells/mm^3. 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, non-response to therapy, or to distinguish from HSV infection. VZV DNA PCR is the most sensitive and specific method for diagnosing VZV infection and can rapidly provide an etiologic diagnosis.[32] In addition to lesion specimens (vesicular fluid or scabs), PCR can be applied to blood, cerebrospinal fluid, aqueous and vitreous humor, and pharyngeal and conjunctival swabs. Laboratories that can differentiate between wild-type and Oka (vaccine)-strain VZV using PCR include the Centers for Disease Control and Prevention (CDC) (404-639-0066), a safety research program sponsored by Merck & Co (1-800-672-6372), and four state public health laboratories (Wisconsin, Minnesota, California, and New York).[33] Prior methods of VZV detection, such as Tzanck smear, direct immunofluorescence for VZV antigen, cell culture, or shell vial culture, are less sensitive and specific than PCR and are no longer readily available.[34,35] Serologic tests are of little value in diagnosing active VZV infection in children with or without HIV, but can be used to determine immunity to VZV.

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 laboratory evidence of immunity) 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.[32,36] Non-immune people (e.g., no clear evidence of vaccination or previous VZV infection) who are exposed to VZV and have a household contact who is living with HIV should receive the varicella vaccine to reduce the chance of introducing wild-type VZV into the household.[37] For the same reason, household contacts aged 50 years and older should receive the HZ vaccine according to Advisory Committee on Immunization Practices (ACIP) recommendations.[38] No precautions are needed following immunization of healthy people who do not develop a rash. However, immunized people who develop a post-immunization rash should avoid direct contact with an immunocompromised host lacking evidence of immunity for the duration of the rash.

Preventing Disease

Active Immunization

Children with HIV stage 3 may develop systemic disease from vaccine-strain VZV; therefore, single-antigen varicella vaccine (VAR; Varivax) **is not recommended** for children with HIV stage 3 **(AIII).**[39] The varicella vaccine can be safely administered to children in whom stable immune reconstitution (see HIV Infection Stage table) is achieved with ART for ≥3 months.[40,41]

Children and adolescents with HIV stage 1 or 2 (see HIV Infection Stage table) without evidence of immunity to varicella should receive two doses of varicella vaccine according to routine or catch-up vaccination schedules **(AI).**[37] The response to varicella vaccination is optimal in children on effective ART for an extended period and in those with high CD4 counts and very low HIV RNA plasma viral loads.[42,43] Limited data from a clinical trial in children 1 to 8 years of age with HIV (CD4 percentage >15%) indicate that the vaccine was well tolerated and that >80% of the children had detectable VZV-specific immune responses (antibody or cell-mediated immune response or both) at 1 year after

vaccination.[39,41] This finding has been validated by other investigators, including persistence of antibodies for 7 years or more post-vaccination.[40,42,44,45] Immunogenicity of the varicella vaccine may decrease as children age, and data are limited on its use in older children and adolescents with HIV. In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered to children with HIV in place of the single-antigen varicella vaccine **(AIII).**

The effectiveness of the varicella vaccine in children with HIV is suggested by long-term follow-up studies of vaccinated children at several institutions.[10,46] In one study, the incidence of primary VZV infection and HZ in the 57 patients who received the VZV vaccine was 22.3 per 1,000 person-years and 4.5 per 1,000 person-years, respectively.[10] In another study, vaccination (one or two doses) was 82% effective against varicella, and no cases of HZ were observed in previously vaccinated children.[46] 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), less fever, and a shorter duration of illness than with varicella in unvaccinated children.[4,47] Comprehensive information on the severity of breakthrough varicella in children with HIV is lacking.

Although children with HIV stage 1 or 2 (see HIV Infection Stage table) tolerate the vaccine well, like healthy children, up to 5% of vaccine recipients may develop a rash 2 to 3 weeks after vaccination. Antiviral therapy is rarely required, and skin lesions usually clear in 3 to 5 days without treatment. Oka (vaccine)-strain VZV is susceptible to acyclovir, should antiviral treatment be necessary. Because low levels of wild-type VZV are still circulating, 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. Oka strain VZV can also cause HZ in vaccinated healthy children, although this occurs less frequently than wild-type HZ among those with natural varicella infection.[14,48] Data on the frequency of Oka strain HZ after vaccination in children with HIV are lacking.

At this time, the recombinant subunit HZ vaccine is licensed only for use in healthy people aged ≥50 years and for adults ≥19 years who are immunodeficient or immunosuppressed, including those with HIV.[38] It has not been studied in children with HIV and should not be given to those aged ≤18 years.

Post-exposure Prophylaxis With Passive Immunization

Children and adolescents with HIV stage 1 or 2 (see HIV Infection Stage table) who lack evidence of immunity to varicella (as defined by ACIP)[37] or who have severe (stage 3; see HIV Infection Stage table) immunosuppression (regardless of prior immunity to varicella) and have a non-transient, significant exposure (e.g., face-to-face exposure for ≥5 minutes) to a person with varicella or HZ should receive varicella-zoster immune globulin (VariZIG) prophylaxis as soon as possible, ideally within 96 hours, but up to 10 days after exposure **(AI).**[49,50] VariZIG, which is administered as a single intramuscular dose, is a purified human varicella-zoster immune globulin made from plasma containing high levels of anti-varicella antibodies (IgG) and is commercially available in the United States from a broad network of specialty distributors (https://www.varizig.com). A large observational study of immunocompromised children without HIV infection indicated that VariZIG given within 72 hours of VZV exposure reduced varicella severity compared to historical controls.[51]

Subsequent studies indicated that some protection occurred with passive immunization for up to 10 days after exposure.[52] Thus, varicella- or HZ-exposed children with HIV are likely to benefit from passive immunization.

Receipt of VariZIG may prolong the incubation period for varicella from 10 to 21 days to up to 28 days, simultaneously extending the period of potential infectiousness. In some cases, VariZIG may attenuate but not prevent varicella.[51] If varicella does not develop, subsequent active immunization with VAR, provided the vaccine is not contraindicated, should be administered 5 months after receipt of VariZIG **(AIII).** If VariZIG is not available, one dose of intravenous immune globulin (IGIV) can be administered once as soon as possible (ideally within 96 hours after exposure). However, the titer of anti-VZV antibodies of any specific lot of IGIV is uncertain because this is not tested routinely. Children who receive IGIV monthly for other indications are likely to be protected from VZV infection if their last dose was received within 3 weeks of varicella or HZ exposure.

Neonates with peripartum exposure to varicella in the immediate peripartum period (onset 5 days before to 48 hours after delivery) may benefit from VariZIG.[33] There are no data to suggest that infants with HIV infection or HIV exposure are at higher risk of neonatal varicella or should be managed differently from infants who have not been exposed to HIV.

Post-exposure Prophylaxis With Antivirals

When passive immunization is not possible for severely immunocompromised individuals, some experts recommend oral acyclovir or valacyclovir for post-exposure prophylaxis (PEP) based on several smaller studies suggesting prevention or attenuation of varicella in healthy children,[53-55] with additional evidence supporting some benefit in immunocompromised children.[56-58] When used for PEP, oral acyclovir or valacyclovir should be initiated 7 days after exposure and continued for 7 days.[33] The use of acyclovir for prophylaxis in VZV-exposed children with HIV has not been studied. For that reason, while some experts recommend using antivirals for PEP, other experts consider it prudent to wait until rash appears to start treatment with acyclovir (or valacyclovir) in VZV-susceptible, VZV-exposed children with HIV who did not receive passive immunization.

Post-exposure Prophylaxis With Varicella Vaccine

Varicella vaccine has been shown to be effective for PEP in children and adults without HIV.[59] However, this preventive approach is predicated on a prompt and robust immune response, which is why it has not been studied or recommended in children with HIV.

Treatment Recommendations

Treating Disease

Based on controlled trials in children with malignancies[60,61] and response to therapy in children with untreated HIV and severe varicella,[19] intravenous (IV) acyclovir is the preferred drug for treating varicella infections in children with HIV, especially those with severe immunosuppression (stage 3—see HIV Infection Stage table) or those who have high fever; abdominal pain; respiratory symptoms; or numerous or deep, necrotic, or hemorrhagic skin lesions **(AI).** IV acyclovir should be initiated as soon as possible after varicella lesions appear, with the greatest benefit demonstrated when initiated within 24 hours of rash onset. In the setting of a national shortage of IV acyclovir, IV ganciclovir or

foscarnet can be substituted. IV antiviral therapy is typically continued for 7 to 14 days, provided that at least 48 hours have elapsed since the appearance of new lesions.

When a child with severe varicella is clinically improved and no new lesions appear, oral therapy can be considered for the remainder of the treatment cycle. Valacyclovir is a prodrug of acyclovir with two- to threefold higher bioavailability when administered orally and is rapidly converted to acyclovir after absorption. Oral valacyclovir is recommended over oral acyclovir for treatment of severe varicella due to its improved bioavailability. For children with HIV stage 1 or 2 (see HIV Infection Stage table) who have mild varicella disease, varicella can be initially treated with oral valacyclovir or oral acyclovir **(BII).** Safety and efficacy data support valacyclovir dosing as young as 3 months of age.[62-65] While no pediatric formulation is available, crushed valacyclovir caplets can be used to make an extemporaneous suspension with good bioavailability.[64-66]

For children ≥3 months of age with HIV and uncomplicated HZ, a 7- to 14-day course of oral valacyclovir is recommended **(AI*).** For children <3 months of age or if oral valacyclovir is unavailable, oral acyclovir can be used. Oral treatment (as opposed to IV) is considered safe for HZ because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. However, initial IV acyclovir administration is recommended for children with HIV stage 3 (see HIV Infection Stage table) and HZ, or with extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ **(AI*).** IV acyclovir may also be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir was demonstrably efficacious in a controlled trial of HZ in immunocompromised adults, including those with disseminated HZ.[67] If treatment is initiated intravenously, it should be continued until cutaneous lesions and visceral disease are clearly resolving, after which oral administration can be considered to complete the 10- to 14-day course of therapy.

Famciclovir is an oral prodrug of penciclovir that is U.S. Food and Drug Administration approved for the treatment of HZ in adults aged ≥18 years. Famciclovir has been evaluated for pediatric use in a single clinical trial of children with varicella (none with HZ), and a sprinkle formulation is available; however, safety and efficacy data are insufficient to support the use of famciclovir in children with HIV <18 years of age who have varicella or HZ.[65,68]

Varicella-Zoster Virus Ocular Disease

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 suspected (e.g., eye pain, conjunctival injection, photophobia, blurred vision). Optimal therapy for VZV-related retinopathy has not been defined. Regardless of VZV-specific 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. Most experts recommend IV anti-VZV therapy that includes combinations of systemic antivirals (e.g., acyclovir or ganciclovir plus foscarnet), frequently given in conjunction with twice-weekly intravitreal injections of ganciclovir and/or foscarnet.[69-71] 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 for 10 to 14 days, followed by prolonged (i.e., 4 to 6 weeks) oral treatment with valacyclovir or acyclovir.[72,73]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Primary toxicities are similar between acyclovir, valacyclovir, and famciclovir and include phlebitis (for IV acyclovir), renal toxicity, nausea, vomiting, and rash. Infants who received high-dose acyclovir for neonatal HSV disease experienced neutropenia (defined as absolute neutrophil count <1,000 cells/mm^3) as a major side effect.[64] However, monitoring for neutropenia is not necessarily indicated for children receiving short courses of acyclovir for varicella or HZ. Among severely ill children without HIV receiving high-dose IV acyclovir, renal injury or failure was observed in >10% of patients.[74] Renal function should be assessed upon initiation of acyclovir treatment and at least once weekly during treatment, especially in children with underlying renal dysfunction who are receiving prolonged therapy. If possible, avoid concomitant administration of other nephrotoxic drugs. Maintaining adequate hydration (via IV fluids if necessary) can help to avoid crystallization of the drug in the renal tubules. IV acyclovir must be adequately diluted and administered slowly over 1 to 2 hours. Dose adjustment based on creatinine clearance is needed in children with renal insufficiency or renal failure (see package insert).

HZ has been considered an IRIS event in numerous reports in which the incidence of HZ was increased transiently after the institution of ART.[75] 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.[11] This suggests that the high incidence of HZ 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[76] and confirmed for HZ.[10]

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.[77] Resistance is rare and primarily occurs in immunocompromised children with inadequate VZV-specific cell-mediated immunity to rapidly clear the VZV infection. If possible, viral isolation in culture or viral sequencing should be attempted to perform susceptibility testing and confirm drug resistance. Because drug susceptibility testing may be difficult to arrange and may involve significant delay, the decision to change therapy should be based clinically. All acyclovir-resistant VZV strains are also resistant to valacyclovir, famciclovir, and ganciclovir and should be treated with IV foscarnet immediately, particularly if clinical status is deteriorating **(AII*).**[72,78] Drugs with a mechanism of action different from viral DNA polymerase inhibition have shown promise in the treatment of acyclovir-resistant VZV, but they are not currently licensed in the United States.[79]

The most common toxicities associated with foscarnet are renal impairment, electrolyte disturbances, and seizures. 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 children with renal insufficiency and can be extrapolated from dose adjustments used for management of CMV (see package insert).[80] Complete blood counts and comprehensive metabolic panels should be monitored in those receiving foscarnet at least two to three 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 those who had wild-type varicella infection.[10,46,81] The recombinant subunit HZ vaccine can be administered to adults with HIV who are ≥19 years of age. In addition, the likelihood of initial or recurrent HZ attacks is reduced with effective ART.[11]

Secondary Prophylaxis

There is no known benefit of secondary prophylaxis (chronic maintenance therapy) for children with HIV after an episode of varicella or HZ.

Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus

Indication	First Choice	Alternative	Comments/Special Issues
Pre-exposure Prophylaxis	VAR (Varivax) vaccine 2-dose series	N/A	VAR is indicated for children aged ≥12 months with HIV stage 1 or 2. VAR is not recommended for children with HIV stage 3. See the Varicella Vaccine section of Figure 1. Recommended Immunization Schedule for detailed vaccine recommendations information.
Primary (Post-exposure) Prophylaxis	Varicella-zoster immune globulin (human [VariZIG]) administered IM, ideally within 96 hours (up to 10 days) after exposure Dosing Based on Body Weight • ≤2 kg: 62.5 international units • 2.1–10 kg: 125 international units • 10.1–20 kg: 250 international units • 20.1–30 kg: 375 international units • 30.1–40 kg: 500 international units • ≥40.1 kg: 625 international units	If VariZIG Is Not Available • IGIV 400 mg/kg actual body weight administered ideally within 96 hours (up to 10 days) after exposure If Passive Immunization Is Not Possible • Consider acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily OR valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7 days, beginning 7 days after exposure.	Primary (Post-exposure) Prophylaxis Is Indicated for— • Children with HIV stage 1 or 2 and substantial exposure to varicella or HZ with no verified history of prior infection, no evidence of vaccination, or who are seronegative for VZV on a sensitive and specific antibody assay; *or* • Children with HIV stage 3 and substantial exposure to varicella or HZ, regardless of immunity history to varicella Note: VariZIG is commercially available in the United States from a broad network of specialty distributors. Varicella vaccine should be administered 5 months after receipt of VariZIG in eligible children. Some experts start acyclovir upon first appearance of rash in children with HIV, rather than providing acyclovir as prophylaxis.
Secondary Prophylaxis	N/A	N/A	There is no indication for secondary prophylaxis.

Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Varicella *Children With Severe Immunosuppression (HIV Stage 3) or Severe Varicella Disease (see* Treating Disease *in text)* • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours for at least 7 days and until no new lesions appear for 48 hours *Children With No or Moderate Immunosuppression (HIV Stage 1 and 2) and Mild Varicella Disease* • If age ≥3 months: o Valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7–14 days • If age <3 months OR unable to obtain valacyclovir suspension: o Acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily for 7–14 days	*Children Unresponsive to Acyclovir When Resistance Is Suspected* • Foscarnet: 120–180 mg/kg/day IV divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours *Children in Whom IV Acyclovir Is Indicated, in the Setting of a National Shortage of IV Acyclovir* • Foscarnet: 120–180 mg/kg/day IV divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours, *or* • Ganciclovir 5 mg/kg/dose IV every 12 hours for at least 7 days and until no new lesions appear for 48 hours	For children aged <2 years, the dose of IV acyclovir is 10 mg/kg/dose every 8 hours. For children aged ≥2 years, some health care providers administer the same dose or base the dose on body surface area (500 mg/m^2/dose IV every 8 hours). When children treated with IV acyclovir show signs of clinical improvement with no new lesions for 48 hours, completion of antiviral therapy with an oral agent may be considered. Renal dose adjustments listed below are only applicable for IV acyclovir: • CrCl >50 mL/minute/1.73 m^2: No dose adjustment necessary • CrCl 25 to 50 mL/minute/1.73 m^2: Administer the usual recommended dose every 12 hours • CrCl 10 to <25 mL/minute/1.73 m^2: Administer the usual recommended dose every 24 hours • CrCl <10 mL/minute/1.73 m^2: Administer 50% of the usual recommended dose every 24 hours (e.g., if the usual recommended dose is 10 mg/kg/dose every 8 hours, then administer 5 mg/kg/dose every 24 hours) • Intermittent hemodialysis: 5 mg/kg/dose IV every 24 hours; administer after hemodialysis on dialysis days • Peritoneal dialysis: 5 mg/kg/dose IV every 24 hours; no supplemental dose needed • Continuous renal replacement therapy: 10 mg/kg/dose IV every 12 hours

Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus

Indication	First Choice	Alternative	Comments/Special Issues
			For patients with renal impairment on PO acyclovir, the Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for adults with renal impairment. In children receiving acyclovir, it is important to maintain adequate hydration to avoid crystallization of the drug in the renal tubules. Valacyclovir doses should be adjusted for renal impairment; however, no formal pediatric renal dosing guidelines exist for valacyclovir. The Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for adults with renal impairment (see package insert). There is no pediatric preparation of valacyclovir, although 500 mg caplets can be extemporaneously compounded to make a suspension. For patients with renal impairment on IV foscarnet, the Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for management of cytomegalovirus.
	Herpes Zoster *Children With Severe Immunosuppression (HIV Stage 3), Trigeminal or Sacral Nerve Involvement, Visceral Involvement, Extensive Multidermatomal, or Disseminated HZ* • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours for 10–14 days	*Children Unresponsive to Acyclovir When Resistance Is Suspected* • Foscarnet IV: 120–180 mg/kg/day divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours	For most cases, oral treatment (as opposed to IV) for HZ is considered safe because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. For renal dose adjustment and other administration considerations with acyclovir, valacyclovir, and foscarnet, see Varicella above.

Dosing Recommendations for Preventing and Treating Varicella-Zoster Virus

Indication	First Choice	Alternative	Comments/Special Issues
	Children With No or Moderate Immunosuppression (HIV Stage 1 and 2) and Uncomplicated HZ • If age ≥3 months: o Valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7–14 days • If age <3 months or unable to obtain valacyclovir suspension: o Acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily for 7–14 days	Famciclovir is approved for use in adults (age ≥18 years) with HZ at a dose of 500 mg/dose PO three times daily for 7–14 days; however, data are insufficient to support the use of famciclovir for HZ in children with HIV.	
	Children With Progressive Outer Retinal Necrosis • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours OR ganciclovir 5 mg/kg/dose IV every 12 hours, *plus* • Foscarnet 90 mg/kg/dose IV every 12 hours, *plus* • Ganciclovir 2 mg/0.05 mL intravitreal twice weekly AND/OR foscarnet 1.2 mg/0.05 mL intravitreal twice weekly *Children With Acute Retinal Necrosis* • Acyclovir 10 mg/kg/dose or 500 mg/m2/dose IV every 8 hours for 10–14 days, **followed by** valacyclovir 20 mg/kg/dose (max: 1,000 g/dose) PO three times daily for 4–6 weeks OR acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily 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. Optimal management of progressive outer retinal necrosis has not been defined.

Key: CrCl = creatinine clearance; HZ = herpes zoster; IGIV = intravenous immune globulin; IM = intramuscular; IV = intravenous; the Panel = Panel on Opportunistic Infections in Children With and Exposed to HIV; PO = oral; VAR = varicella; VZV = varicella-zoster virus

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Appendix A. Key to Acronyms

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

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: November 21, 2024
Reviewed: November 21, 2024

NIH-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), plus approximately 46 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 and in collaboration with the HIV Medicine Association of the Infectious Disease Society of America (HIVMA/IDSA), the Pediatric Infectious Disease Society (PIDS), and the American Academy of Pediatrics (AAP)
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

Updated: April 23, 2026
Reviewed: April 23, 2026

Section	Panel Members
Introduction	Bill G. Kapogiannis, MD U.S. Department of Health and Human Services Administration for Strategic Preparedness and Response Washington, DC
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Candida Infections	Dallas Smith, PharmD** Centers for Disease Control and Prevention Atlanta, GA
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Coccidioidomycosis	John Christenson, MD* Indiana University School of Medicine Indianapolis, IN
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COVID-19	Susan Carr, PharmD, AAHIVP** St. Jude Children's Research Hospital Memphis, TN
Cryptococcosis	Dallas Smith, PharmD** Centers for Disease Control and Prevention Atlanta, GA

Section	Panel Members
Cytomegalovirus Infection	Meganne Kanatani, PharmD, BCIDP** Ronald Reagan UCLA Medical Center Los Angeles, CA
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Histoplasmosis	John Christenson, MD* Indiana University School of Medicine Indianapolis, IN
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Human Papillomavirus Disease	Susan Carr, PharmD, AAHIVP** St. Jude Children's Research Hospital Memphis, TN
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	Patricia Flynn, MD St. Jude Children's Research Hospital Memphis, TN
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Syphilis	Kevin O'Callaghan, MBBCh, BAO* Centers for Disease Control and Prevention Atlanta, GA
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Toxoplasmosis	Mariam Aziz, MD Rush University Medical Center Chicago, IL
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Varicella-Zoster Virus Disease	Gustavo Alvira-Arill, PharmD, BCPPS, BCIDP** Medical University of South Carolina Charleston, SC
	Gail Demmler-Harrison, MD Baylor College of Medicine Texas Children's Hospital Houston, TX
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Appendix D. Financial Disclosures

Updated: April 23, 2026
Reviewed: April 23, 2026

Panel Member	Section	Company	Relationship
Gustavo Alvira-Arill Medical University of South Carolina Charleston, SC	Herpes Simplex Virus Infection, Immunization, Parasitic Infections, Varicella-Zoster Virus Disease	None	N/A
Mariam Aziz Rush University Medical Center Chicago, IL	*Mycobacterium avium* Complex Disease, Toxoplasmosis	Syneos Health	Data Safety Monitoring Board Member
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		Merck & Co.	Research Support
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		Moderna	Research Support
		MicroGen Diagnostics	Research Support
		Medscape (WebMD)	Speakers' Bureau
		Wolters Kluwer (UpToDate)	Royalties

Panel Member	Section	Company	Relationship
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		Sanofi Pasteur	Research Support
		Meissa Vaccines	Research Support
		Bavarian Nordic	Research Support
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Gabriela Marón St. Jude Children's Research Hospital Memphis, TN	Parasitic Infections	None	N/A
James McAuley The University of Arizona College of Medicine – Tucson Tucson, AZ	*Mycobacterium avium* Complex Disease, Toxoplasmosis	None	N/A
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			Research Support
		Stellus Rx	Research Support
		Basilea Pharmaceutica	Advisory Board
		Copeland, Stair, Valz & Lovell, LLP	Expert Witness Testimony
		Infectious Diseases Special Edition	Honoraria
		Managed Healthcare Executive	Honoraria
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Julie Richardson St. Jude Children's Research Hospital Memphis, TN	Hepatitis B Virus Infection, Hepatitis C Virus Infection, Pharmacology Review (Tables 4 and 5)	None	N/A
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		ViiV Healthcare	Research Support
		Moderna	Research Support
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		Merck & Co.	Research Support
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Kristy M. Shaeer University of South Florida Tampa, FL	*Mycobacterium tuberculosis,* Parasitic Infections, Syphilis, Toxoplasmosis	None	N/A
Masako Shimamura Nationwide Children's Hospital Columbus, OH	Cytomegalovirus Infection	None	N/A
Dallas Smith Centers for Disease Control and Prevention Atlanta, GA	*Candida* Infections, Coccidioidomycosis, Cryptococcosis, Histoplasmosis	None	N/A
Kathy Tassiopoulos Harvard T.H. Chan School of Public Health Jamaica Plain, MA	Human Papillomavirus Disease	None	N/A

Panel Member	Section	Company	Relationship
Brenda Tesini University of Rochester School of Medicine and Dentistry Rochester, NY	*Pneumocystis* Pneumonia	Merck & Co.	Honoraria
Jill Weatherhead Baylor College of Medicine Houston, TX	Parasitic Infections	None	N/A
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Dwight Yin National Institutes of Health Rockville, MD	*Candida* Infections	None	N/A

Consultant	Section	Company	Relationship
Moherndran Archary University of KwaZulu-Natal Durban, South Africa	Cryptococcosis	None	N/A
Eva Clark Baylor College of Medicine Houston, TX	Parasitic Infections	None	N/A
Rachel Martin-Blais Nationwide Children's Hospital Columbus, OH	Parasitic Infections	Children's Hospital of Philadelphia Health Professionals	Advisory Board
		Merck & Co.	Other
		Organon	Research Support
		General Electric	Research Support
James Wood Indiana University School of Medicine, Indianapolis, IN	Histoplasmosis	None	N/A

Contributor	Section	Company	Relationship
Collin Dubick Emory University School of Medicine Atlanta, GA	*Mycobacterium tuberculosis*	None	N/A
Evan Shirey The Johns Hopkins University School of Medicine Baltimore, MD	*Mycobacterium tuberculosis*	None	N/A

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
- Mpox
- 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? • Antibody (or DNA testing) for HHV-8 is insufficiently sensitive/specific to predict risk of Kaposi sarcoma. Therefore, routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended (strong, very low). II. Among HIV-infected children, does initiation of antiretroviral therapy (ART) (as compared with non-initiation) reduce the risk of Kaposi sarcoma? • Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated Kaposi sarcoma (strong, low). III. For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of Kaposi sarcoma? • Data are insufficient and conflicting upon which to base a recommendation for a particular ART regimen for prevention of Kaposi sarcoma (weak, low). IV. Among HIV-infected children with active Kaposi sarcoma, is treatment with ART (as compared with no ART) associated with higher rates of remission and/or decreased mortality? • Treatment with ART is associated with increased survival among HIV-infected children with active Kaposi sarcoma. Effective suppression of HIV replication with ART is recommended for all patients with evidence of active Kaposi sarcoma and other HHV-8-associated malignant lymphoproliferative disorders (strong, very low). V. Among HIV-infected children with active Kaposi sarcoma, is treatment with chemotherapy in addition to ART (as compared with ART alone) associated with higher rates of remission and/or decreased mortality? • Systemic chemotherapy, in addition to ART, is associated with higher rates of remission and decreased mortality and is recommended for disseminated or visceral Kaposi sarcoma (stage T1 disease) and for primary effusion lymphoma (strong, low). For localized Kaposi sarcoma (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear. VI. Among HIV-infected children treated with ART who develop immune reconstitution inflammatory syndrome (IRIS), is chemotherapy in addition to continuation of ART (compared with no chemotherapy) associated with higher rates of remission and/or decreased mortality? • For patients with Kaposi-sarcoma-associated IRIS, chemotherapy along with continuation of ART is recommended (strong, low). VII. Among HIV-infected children who achieve remission from Kaposi sarcoma, what therapies are recommended to lower the risk of recurrence? • Effective suppression of HIV replication with ART in HIV-infected patients with Kaposi sarcoma may prevent Kaposi sarcoma progression or occurrence of new lesions and may decrease risk of recurrence after remission. Life-long ART is recommended for all individuals with evidence of active or treated Kaposi sarcoma or other HHV-8-associated malignant lymphoproliferative disorders (strong, low).
Rating System *Strength of Recommendation: Strong; Weak* *Quality of Evidence: High; Moderate; Low; or Very Low*

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
I. Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)? • 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). • 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). • 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)? • 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). • 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). • 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)? • 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). • 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. • 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).

Rating System

Strength of Recommendation: Strong; Weak

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

[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) Influenza A and B	Oseltamivir • Aged <3 Months: Not recommended[a] • Aged 3 Months to <1 Year: Oseltamivir 3mg/kg body weight/dose once daily[a] • Aged ≥1 to 12 Years: Weight-band dosing[a] o Weighing ≤15 kg: Oseltamivir 30 mg once daily o Weighing >15 kg to 23 kg: Oseltamivir 45 mg once daily o Weighing >23 kg to 40 kg: Oseltamivir 60 mg once daily o Weighing >40 kg: Oseltamivir 75 mg once daily • Aged ≥13 Years: Oseltamivir 75 mg once daily Zanamivir (Aged **≥5** Years) • Zanamivir 10 mg (2 inhalations) once daily[b]	None	Pre-Exposure Chemoprophylaxis *Indications* • 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. *Duration* • When employed, pre-exposure antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community. Post-Exposure Chemoprophylaxis *Indications Recommended For:* • Children with HIV with severe immunosuppression regardless of influenza vaccination status. • Children with HIV with moderate to no immunosuppression if o Influenza vaccination is contraindicated or unavailable; *or* o Low influenza vaccine effectiveness is documented in the current influenza season; *and* o Antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza. *Duration* 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. • If influenza vaccination is provided after contact, chemoprophylaxis duration should be 2 weeks after vaccination.

			• If exposure is to a household contact, chemoprophylaxis duration should be 7 days. • 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] Oseltamivir Dosing Adjustments *Premature Infants* • Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).[d] *Renal Insufficiency* • 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 Influenza A and B	Oseltamivir[e] • Aged <3 Months: Oseltamivir 3mg/kg/dose twice daily • Aged 3 Months to <1 Year: Oseltamivir 3 mg/kg/dose twice daily • Aged ≥1 to 12 Years: Weight-band dosing o Weighing ≤15 kg: Oseltamivir 30 mg twice daily o Weighing >15 kg to 23 kg: Oseltamivir 45 mg twice daily o Weighing >23 kg to 40 kg: Oseltamivir 60 mg twice daily	None	*Duration* • 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] Oseltamivir Dosing Adjustments *Premature Infants* • Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).[d] *Renal Insufficiency* • Oseltamivir renal dosing is not well established for pediatric patients. For children >40 kg, adult renal dosing can be used.

	○ Weighing >40 kg: Oseltamivir 75 mg twice daily • Aged ≥13 Years: Oseltamivir 75 mg twice daily Zanamivir (Aged ≥7 Years) • Zanamivir 10 mg (2 inhalations) twice daily[f]		CrCl/Dose • 61–90 mL/minute: 75 mg twice daily • 31–60 mL/minute: 30 mg twice daily • 11–30 mL/minute: 30 mg once daily • ≤10 mL/minute, ESRD on hemodialysis: 30 mg dose after every hemodialysis cycle • ≤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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Mpox

Updated: April 23, 2026
Reviewed: April 23, 2026

On July 23, 2022, the World Health Organization declared mpox a global health emergency. Monkeypox virus (abbreviated as MPXV) is a member of the Poxviridae family (genus Orthopoxvirus). The first case of mpox identified in the United States as part of the recent outbreaks was confirmed in May 2022, and mpox was declared a public state of emergency in the United States from August 4, 2022, to January 31, 2023. This serious emerging outbreak is currently more common among gay, bisexual, and other men who have sex with men than among the general population. Sporadic cases have been reported in children and pregnant women. To date, no definitive data show 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 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. 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. Online resources for checking drug interactions include the Liverpool HIV Drug Interactions Checker and the Drug–Drug Interaction Guide.

JYNNEOS, an effective, FDA-approved, live attenuated, non-replicating smallpox and mpox vaccine, can be used for pre- and post-exposure prophylaxis in people with HIV. 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. ACAM2000, a live replicating smallpox and mpox vaccine, is not recommended for people with HIV. Vaccinia immune globulin intravenous (or VIGIV) is available through an investigational drug protocol for infants aged under 6 months. For mpox immunization recommendations, see Figure 1. Recommended Immunization Schedule.

The Mpox and Immunization chapters of the Adult and Adolescent Opportunistic Infection Guidelines provide clinical guidance for the prevention and treatment of mpox in adults and adolescents with HIV.

The most comprehensive source of information about the prevention and treatment of mpox can be found on CDC's Clinical Guidance webpage, which includes clinical considerations for immunocompromised people and children and adolescents, as well as mpox clinical care and treatment during pregnancy. Additional resources can be found on Infectious Diseases Society of America's Mpox webpage.

Progressive Multifocal Leukoencephalopathy

Updated: October 6, 2013
Reviewed: October 6, 2013

Panel's Recommendations
• The main approach to treatment of Progressive Multifocal Leukoencephalopathy (PML) is treatment with an effective antiretroviral regimen that suppresses HIV viremia and preserves or restores CD4 T lymphocyte (CD4) cell-defined immune function (AII). • Intrathecal cytosine arabinoside and cidofovir are not routinely recommended for treatment of PML (BIII). • Immunomodulatory approaches, such as interferon alfa, are not routinely recommended for treatment of PML (BIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *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

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: April 23, 2026
Reviewed: April 23, 2026

Indication	First Choice	Alternative	Comments/Special Issues
Bacterial Infections (*S. pneumoniae* and other invasive bacteria)	• Pneumococcal, meningococcal, and Hib vaccines • IVIG 400 mg/kg body weight every 2–4 weeks (only in cases of hypogammaglobulinemia, IgG <400 mg/dL)	TMP-SMX, 75/375 mg/m^2 BSA per dose by mouth twice daily	See CDC website for detailed immunization schedule. Criteria for Discontinuing IVIG • Resolution of hypogammaglobulinemia Criteria for Restarting IVIG • Relapse of hypogammaglobulinemia
Candida Infections	Not routinely recommended	N/A	N/A
Coccidioidomycosis	N/A	N/A	Primary prophylaxis is not routinely indicated in children.
COVID-19	COVID-19 vaccines and updated vaccines	Pemivibart (Pemgarda) *Aged ≥12 Years and ≥40 kg* • Pemivibart injection solution: 4,500 mg administered as a single IV infusion	COVID-19 Vaccination Indicated for— • All children with HIV aged ≥6 months regardless of CD4 cell count or viral load • Household members and close contacts of children with HIV aged ≥6 months For up-to-date vaccine guidance, see CDC's Use of COVID-19 Vaccines in the United States webpage. Children with HIV may qualify for additional doses of COVID-19 vaccines if they have stage 3 HIV infection, history of an AIDS-defining illness without immune reconstitution, clinical manifestations of symptomatic HIV, or untreated HIV infection. Pemivibart Indicated for— • Adults and adolescents aged ≥12 years and who weigh ≥40 kg with moderate-to-severe immunocompromise

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			(including those with advanced or untreated HIV infection) who are unlikely to have an adequate response to COVID-19 vaccination.
Cryptococcosis	Not recommended	Not recommended	N/A
Cryptosporidiosis	ARV therapy to avoid advanced immune deficiency	N/A	N/A
Cytomegalovirus Infection (CMV)	• For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food • 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— • 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). Criteria for Discontinuing Primary Prophylaxis • Age ≥6 years with CD4 count >100 cells/mm^3 • Age <6 years with CD4 percentage >10% Criteria for Considering Restarting Primary Prophylaxis • Age ≥6 years with CD4 count <50 cells/mm^3 • Age <6 years with CD4 percentage <5%
Giardiasis	ART to avoid advanced immunodeficiency	N/A	N/A
Hepatitis B Virus Infection (HBV)	All Children • HepB vaccine Infants Born to Women With HBV • HepB vaccine plus HBIG	HBIG following exposure	See Figure 1. Recommended Immunization Schedule for detailed vaccine recommendations. Primary Prophylaxis Indicated for— • All individuals who are not infected with HBV Criteria for Discontinuing Primary Prophylaxis • N/A

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			Criteria for Restarting Primary Prophylaxis • N/A
Hepatitis C Virus Infection (HCV)	N/A	N/A	N/A
Herpes Simplex Virus Infection (HSV)	N/A	N/A	Primary prophylaxis not indicated
Histoplasmosis	N/A	N/A	Primary Prophylaxis Indicated for— • Selected HIV-infected adults but not children Criteria for Discontinuing Primary Prophylaxis • N/A Criteria for Restarting Primary Prophylaxis • N/A
Human Papillomavirus Disease (HPV)	HPV vaccine	N/A	See Figure 1. Recommended Immunization Schedule for detailed vaccine recommendations.
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.

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Malaria	For Travel to Chloroquine-Sensitive Areas: • 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. • Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home o 11–20 kg; one pediatric tablet (62.5 mg/25 mg) o 21–30 kg, two pediatric tablets (125 mg/50 mg) o 31–40 kg; three pediatric tablets (187.5 mg/75 mg) o >40 kg; one adult tablet (250 mg/100 mg) • 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. • Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg)	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/. 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*. G6PD screening must be performed prior to primaquine use. Chloroquine phosphate is the only formulation of chloroquine available in the United States; 10 mg of chloroquine phosphate = 6 mg of chloroquine base. 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
	For Areas With Mainly *P. Vivax:* • 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 For Travel to Chloroquine-Resistant Areas: • Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home o 11–20 kg; one pediatric tablet (62.5 mg/25 mg) o 21–30 kg; two pediatric tablets (125 mg/50 mg) o 31–40 kg; three pediatric tablets (187.5 mg/75 mg) o >40 kg; one adult tablet (250 mg/100 mg) • 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. • Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg)		
Microsporidiosis	N/A	N/A	Not recommended

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Mycobacterium avium Complex (MAC)	• Clarithromycin 7.5 mg/kg (maximum 500 mg/dose) PO twice daily, *or* • Azithromycin 20 mg/kg (maximum 1,200 mg) PO once weekly Note: Careful monitoring of drug–drug interactions is critical when using clarithromycin in children on ARVs.	• Azithromycin 5 mg/kg (maximum 250 mg) PO once daily • For children who cannot tolerate azithromycin or clarithromycin, rifabutin (5 mg/kg/daily, maximum dose 300 mg) is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use.	Primary Prophylaxis Indicated for Children With HIV Who Have Advanced Immunosuppression, as Defined by CD4 Count Below, and Who Are Not on a Fully Suppressive ARV Regimen • *Aged <1 Year:* CD4 count <750 cells/mm^3 • *Aged 1 to 5 Years:* CD4 count <500 cells/mm^3 • *Aged ≥6 Years:* CD4 count <200 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis • Do not discontinue in children aged <2 years. • After ≥6 months of ART, *and* o *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for >3 consecutive months o *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for >3 consecutive months Criteria for Restarting Primary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3
Mycobacterium tuberculosis Treatment of LTBI, Also Known as TB Preventive Therapy	Source Case Drug Susceptible • Age 2 to <12 years 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)	• Rifampin 15–20 mg/kg (max 600 mg) daily for 4 months duration, *or* • Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 15–20 mg/kg (maximum 600 mg/day) for 3 months duration, *or* • Isoniazid 10–15 mg/kg (max 300 mg) daily for 6–9 months	Indications • Positive TST (TST ≥5 mm in children with HIV) or IGRA without previous TB treatment • Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis) Considerations • TB disease must be excluded before starting treatment for latent TB infection.

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• Age ≥12 years 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) Source Case Drug Resistant • For isoniazid-resistant source cases, daily rifampin 15–20 mg/kg (maximum 600 mg/day) for 4 months is recommended. • For isoniazid- and rifampin-resistant (i.e., MDR-TB) source cases, consult a TB expert and local public health authorities.		• Drug–drug interactions with ART should be considered for all rifamycin-containing alternatives. Criteria for Discontinuing Prophylaxis • Only with documented severe adverse event, such as hepatotoxicity, hypersensitivity, or other adverse drug reactions, which are rare in children and adolescents. Adjunctive Treatment • 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 girls and women.
Pneumocystis Pneumonia	• TMP-SMX: 5–10 mg/kg/DAY (TMP component) • Maximum individual dose: 160 mg/DOSE (TMP component). • Several dosing regimens have been used successfully: o 3 days per week on consecutive or alternate days in divided doses every 12 hours o Daily as a single dose o Administration 2 days per week on consecutive or alternate	Dapsone and atovaquone are both first-line alternatives (see text for relative risks and benefits), followed by aerosolized pentamidine as second line and IV pentamidine as third line. Dapsone • *Children Aged ≥1 Month:* 2 mg/kg/dose (maximum: 100 mg/dose) PO once daily or 4 mg/kg/dose (maximum 200 mg/dose) PO once weekly	Primary Prophylaxis Indicated for— • All infants with HIV or in whom HIV infection cannot be presumptively excluded beginning from age 4–6 weeks to 12 months, regardless of CD4 count or percentage • Children With Stage 3 CD4 Count (see HIV Infection Stage Table for more information): o *Children Aged 1 Year to <6 Years:* <500 cells/mm^3 or <22% o *Children Aged ≥6 Years:* <200 cells/mm^3 or <14% Criteria for Discontinuing Primary Prophylaxis • *Children Aged <1 Year:* Continue primary prophylaxis in children with HIV throughout the first year of life

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	days in doses divided every 12 hours has been used successfully in pediatric oncology patients.	Atovaquone • *Children Aged 1–3 Months or >24 Months to 12 Years:* 30–40 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged ≥13 Years:* 1,500 mg PO once daily Aerosolized Pentamidine Via Respirgard II Nebulizer *For Children Able to Comply With Its Use:* • *Children Aged <5 Years:* Limited data regarding dosing. 9 mg/kg/dose or 150 mg/dose every month have been suggested. • *Children Aged ≥5 Years:* 300 mg every month IV Pentamidine • 4 mg/kg/dose every 3–4 weeks; maximum dose: 300 mg/dose • Limited data regarding dosing frequency; based on use in oncology patients	• Children Aged 1 Year and Older on ART for ≥6 Months With CD4 Count Above Age-Specific Stage 3 Cutoff for >3 Consecutive Months: o *Children Aged 1 Year to <6 Years:* ≥500 cells/mm^3 or ≥22% o *Children Aged ≥6 Years:* ≥200 cells/mm^3 or ≥14% • Discontinuation can be considered in children ≥6 Years if on ART for ≥6 months with undetectable viral load and CD4 count 101–200 cells/mm^3 if intolerant of prophylaxis medications Criteria for Restarting Primary Prophylaxis • CD4 count below age-specific stage 3 cutoff (see above)

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Syphilis	N/A	Same as for primary prophylaxis.	Primary Prophylaxis Indicated for— • N/A Criteria for Discontinuing Primary Prophylaxis • N/A Criteria for Restarting Primary Prophylaxis • N/A
Toxoplasmosis	TMP-SMX 150/750 mg/m^2 BSA once daily PO	**For Children Aged ≥1 Month:** • Dapsone 2 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO every 3 days (continued for 1 week after pyrimethamine completed due to long half-life) For Children Aged 1–3 Months and >24 Months: • Atovaquone 30 mg/kg body weight (maximum 1,500 mg) PO once daily with food For Children Aged 4–24 Months:	Primary Prophylaxis Indicated for— *Children With IgG Antibody to Toxoplasma and Severe Immunosuppression Who Are:* • Aged <1 year with CD4% ≤26% or CD4 ≤750 cells/mm^3, *or* • Aged 1–5 years with CD4% ≤22% or CD4 ≤500 cells/mm^3, *or* • Aged ≥6 years with CD4 count ≤100 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis Note: Do not discontinue in children aged <1 year. • Aged 1–5 years with CD4 count >500 cells/mm^3 for >3 consecutive months *or* • Aged ≥6 years with CD4 count >200 cells/mm^3 for >3 consecutive months Criteria for Restarting Primary Prophylaxis: • Aged 1–5 years with CD4 count <500 cells/mm^3 *or* • Aged ≥6 years with CD4 count <200 cells/mm^3

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		• Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *with or without* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* leucovorin 5 mg PO every 3 days Acceptable Alternative Dosage Schedules for TMP-SMX • TMP-SMX 150/750 mg/m^2 BSA per dose PO three times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/m^2 BSA per dose twice daily PO every day • TMP-SMX 75/375 mg/m^2 BSA per dose twice daily PO three times weekly on alternate days	
Varicella-Zoster Virus Disease (VZV) Pre-exposure Prophylaxis	VAR (Varivax) vaccine 2-dose series	N/A	VAR is indicated for children aged ≥12 months with HIV stage 1 or 2. VAR is **not recommended** for children with HIV stage 3. See the Varicella Vaccine section of Figure 1. Recommended Immunization Schedule for detailed vaccine recommendations information.
Varicella-Zoster Virus Disease (VZV) Primary (Post-exposure) Prophylaxis	Varicella-zoster immune globulin (human [VariZIG]) administered IM, ideally within 96 hours (up to 10 days) after exposure	If VariZIG Is Not Available • IGIV 400 mg/kg actual body weight administered ideally within 96	Primary (Post-exposure) Prophylaxis Is Indicated for— • Children with HIV stage 1 or 2 and substantial exposure to varicella or HZ with no verified history of prior infection, no

Table 1. Primary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	Dosing Based on Body Weight • ≤2 kg: 62.5 international units • 2.1–10 kg: 125 international units • 10.1–20 kg: 250 international units • 20.1–30 kg: 375 international units • 30.1–40 kg: 500 international units ≥40.1 kg: 625 international units	hours (up to 10 days) after exposure If Passive Immunization Is Not Possible Consider acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily OR valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7 days, beginning 7 days after exposure.	evidence of vaccination, or who are seronegative for VZV on a sensitive and specific antibody assay; *or* • Children with HIV stage 3 and substantial exposure to varicella or HZ, regardless of immunity history to varicella Note: VariZIG is commercially available in the United States from a broad network of specialty distributors. Varicella vaccine should be administered 5 months after receipt of VariZIG in eligible children. Some experts start acyclovir upon first appearance of rash in children with HIV, rather than providing acyclovir as prophylaxis.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BSA = body surface area; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; CrCl = creatinine clearance; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HepB = hepatitis B [vaccine]; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IgG = immunoglobulin G; IGRA = interferon-gamma release assay; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; LTBI = latent TB infection; MDR-TB = multidrug-resistant tuberculosis; PO = orally; 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: April 23, 2026
Reviewed: April 23, 2026

Indication	First Choice	Alternative	Comments/Special Issues
Bacterial Infections (*S. pneumoniae* and other invasive bacteria)	TMP-SMX 75/375 mg/m^2 BSA per dose by mouth twice daily	IVIG 400 mg/kg body weight every 2–4 weeks	Secondary Prophylaxis Indicated • More than two serious bacterial infections in a 1-year period in children who are unable to take ART Criteria for Discontinuing Secondary Prophylaxis • 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) Criteria for Restarting Secondary Prophylaxis • More than two serious bacterial infections in a 1-year period despite ART
Candida Infections	Not routinely recommended but can be considered for frequent severe recurrences despite ART. • Fluconazole 6 mg/kg body weight (maximum 200 mg/dose) PO three times weekly	• Fluconazole 3–6 mg/kg body weight PO daily (maximum 200 mg/day) • Itraconazole oral solution, 2.5 mg/kg body weight/dose PO twice daily	Secondary Prophylaxis Indicated (Limited Data in Children) • Frequent or severe recurrences despite ART • In patients with initial fluconazole-refractory OPC or esophageal candidiasis that subsequently responded to voriconazole, posaconazole, or an echinocandin: may consider continuation of the effective drug until immune reconstitution Criteria for Discontinuing Secondary Prophylaxis • When CD4 count or percentage has risen to HIV stage 1 or 2 (see HIV Infection Stage Table) Criteria for Restarting Secondary Prophylaxis

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			• Frequent severe recurrences
Coccidioidomycosis	• Fluconazole 6 mg/kg body weight (maximum 400 mg) per dose IV or PO once daily, *or* • For Coccidioidal Meningitis: o Continue initial treatment with fluconazole (12 mg/kg body weight per dose IV or PO once daily)	Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily	Secondary Prophylaxis Indicated • Prior meningitis or disseminated disease • Milder disease if CD4 count <250 cells/mm^3 or CD4 percentage <15%. Criteria for Discontinuing Secondary Prophylaxis • Lifelong therapy for meningitis or disseminated disease • Consider lifelong therapy for milder disease, regardless of ART or immune reconstitution
COVID-19	N/A	N/A	N/A
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 • Documented disease Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria Are Fulfilled* • Age ≥6 years • Asymptomatic on ≥12 months of secondary prophylaxis • CD4 count ≥100 cells/mm^3 with undetectable HIV viral load on ART for >3 months Criteria for Restarting Secondary Prophylaxis • CD4 count <100/mm^3 [a] Secondary prophylaxis is also referred to as maintenance therapy or suppressive therapy.

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Cryptosporidiosis	N/A	N/A	N/A
Cytomegalovirus Infection (CMV)	• Ganciclovir 5 mg/kg body weight IV once daily; *or* • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food; *or* • 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* • 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— • Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse. Criteria for Discontinuing Secondary Prophylaxis (All of the Following Criteria Must Be Fulfilled) • Completed ≥6 months of ART • Age <6 years with CD4 percentage ≥15% for >6 consecutive months • Age ≥6 years with CD4 count >100 cells/mm^3 for >6 consecutive months • Consultation with ophthalmologist (if retinitis) o Routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis. Criteria for Restarting Secondary Prophylaxis • Age <6 years with CD4 percentage <15% • Age ≥6 years with CD4 count <100 cells/mm^3
Giardiasis	N/A	N/A	N/A
Hepatitis B Virus Infection (HBV)	HepA vaccine	N/A	Secondary Prophylaxis Indicated for— • Individuals with chronic HBV infection to prevent further liver injury. Criteria for Discontinuing Secondary Prophylaxis • N/A

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			Criteria for Restarting Secondary Prophylaxis • N/A
Hepatitis C Virus Infection (HCV)	N/A	N/A	N/A
Herpes Simplex Virus (HSV) Infection	Mucocutaneous Disease • Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth twice daily Suppressive Therapy After Neonatal HSV Disease (Skin, Eye, Mouth, CNS, or Disseminated Disease) • Acyclovir 300 mg/m^2 BSA/dose by mouth three times daily for 6 months	Mucocutaneous Disease, for Adolescents Old Enough to Receive Adult Dosing • Valacyclovir 500 mg by mouth twice daily, *or* • Famciclovir 500 mg by mouth twice daily	Secondary Prophylaxis Indicated • Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease. Criteria for Discontinuing Secondary Prophylaxis • 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.
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 • Documented histoplasmosis in a patient with impaired immune function Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria Are Fulfilled* • CD4 percentage >15% at any age; or CD4 cell count >150 cells/mm^3 aged ≥6 years • Received ≥1 year itraconazole maintenance therapy • Established (e.g., ≥6 months) adherence to effective ART • Negative *Histoplasma* blood cultures

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			• Serum Histoplasma antigen <2 ng/mL 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 Disease (HPV)	N/A	N/A	N/A
Isosporiasis (Cystoisosporiasis)	If Severe Immunosuppression— • 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. Second-Line Alternative • 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. 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. 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.
Malaria	For *P. vivax* or *P. ovale* • 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	N/A	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. http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#1939

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Microsporidiosis	Disseminated, Non-ocular Infection or GI Infection Caused by Microsporidia Other Than *E. bieneusi* or *V. corneae* • Albendazole 7.5 mg/kg body weight (maximum 400 mg/dose) by mouth twice daily Ocular Infection • 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 four times a day (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 • After initiation of ART, resolution of signs and symptoms and sustained immune reconstitution (more than 6 months at CDC immunologic category 1 or 2)
Mycobacterium avium Complex (MAC) (Chronic Suppressive Therapy)	• Clarithromycin[a] 7.5 mg/kg body weight (maximum 500 mg/dose) PO twice daily, *plus* • Ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) PO once daily, with or without food • *For Children Aged ≥6 Years Who Received Rifabutin as Part of Initial Treatment:* rifabutin[a] 5 mg/kg	• Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily, *plus* • Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food • *For Children Aged ≥6 Years Who Received Rifabutin as Part of Initial Treatment:* rifabutin[a] 5 mg/kg	Secondary Prophylaxis Indicated • Prior disease Criteria for Discontinuing Secondary Prophylaxis • Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence. • There are limited data to recommend discontinuation of secondary prophylaxis in children aged <2 years. However, if continuation of secondary prophylaxis for

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	(maximum 300 mg) PO once daily with food	(maximum 300 mg) PO once daily with food	MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate. *Fulfillment of All of the Following Criteria* • Completed ≥6 months of stable ART, *and* • Completed ≥12 months of MAC therapy, *and* • Asymptomatic for signs and symptoms of MAC, *and either* • *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for ≥6 consecutive months, *or* • *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for ≥6 consecutive months Criteria for Restarting Secondary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3
Mycobacterium tuberculosis	N/A	N/A	N/A
Pneumocystis Pneumonia	• TMP-SMX: 5–10 mg/kg/DAY (TMP component) • Maximum individual dose: 160 mg/DOSE (TMP component). • Several dosing regimens have been used successfully: o 3 days per week on consecutive or alternate days in divided doses every 12 hours o Daily as a single dose o Administration 2 days per week on consecutive or alternate days	Dapsone and atovaquone are both first-line alternatives (see text for relative risks and benefits), followed by aerosolized pentamidine as second line and IV pentamidine as third line. Dapsone • *Children Aged ≥1 Month:* 2 mg/kg/dose (maximum: 100 mg/dose) PO once daily or 4 mg/kg/dose (maximum 200 mg/dose) PO once weekly	Secondary Prophylaxis Indicated for: • Children with prior episode of PCP Criteria for Discontinuing Secondary Prophylaxis • *Children Aged <1 Year:* Continue primary prophylaxis in children with HIV throughout the first year of life • *Children Aged 1 Year and Older on ART for ≥6 Months With CD4 Count Above Age-Specific Stage 3 Cutoff for >3 Consecutive Months:* o *Children Aged 1 Year to <6 Years:* ≥500 cells/mm^3 *or* ≥22%

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	in doses divided every 12 hours has been used successfully in pediatric oncology patients.	Atovaquone • *Children Aged 1–3 Months or >24 Months to 12 Years:* 30–40 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged ≥13 Years:* 1,500 mg PO once daily Aerosolized Pentamidine Via Respirgard II Nebulizer *For Children Able to Comply With Its Use* • *Children Aged <5 Years:* Limited data regarding dosing. 9 mg/kg/dose or 150 mg/dose every month have been suggested. • *Children Aged ≥5 Years:* 300 mg every month IV Pentamidine • 4 mg/kg/dose every 3 to 4 weeks; maximum dose: 300 mg/dose • Limited data regarding dosing frequency; based on use in oncology patients	o *Children Aged ≥6 Years:* ≥200 cells/mm^3 or ≥14% • Discontinuation can be considered in children ≥6 Years if on ART for ≥6 months with undetectable viral load and CD4 count 101–200 cells/mm^3 if intolerant of prophylaxis medications Criteria for Restarting Secondary Prophylaxis • CD4 count below age-specific stage 3 cutoff (see above)

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Syphilis	N/A	N/A	Secondary Prophylaxis Indicated • N/A Criteria for Discontinuing Secondary Prophylaxis • N/A Criteria for Restarting Secondary Prophylaxis • N/A
Toxoplasmosis (Suppressive Therapy)	• Sulfadiazine 85–120 mg/kg body weight per day in 2–4 divided doses (maximum 2–4 g per day) PO, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days	• Clindamycin 7–10 mg/kg body weight per dose (max 600 mg/dose) PO three times daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days Children Aged 1–3 Months and >24 Months • Atovaquone 30 mg/kg body weight PO (maximum 1,500 mg) once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 BSA PO once daily Children Aged 4–24 Months *Option 1* • Atovaquone 45 mg/kg body weight PO once daily with food, *with or without*	Secondary Prophylaxis Indicated • Prior TE Note: Limited data in children is available for alternative regimens. TMP-SMX only to be used if individual is intolerant to other regimens. Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria Are Fulfilled*: • Completed initial therapy for TE, *and* • Asymptomatic for TE, *and* • Aged ≥6 years old with CD4 >200 cells/mm^3 in those or CD4% >22% (CD4 count >500 cells/mm^3) in those aged 1–5 years for 3 consecutive months Criteria for Restarting Secondary Prophylaxis: • CD4 count ≤200 cells/mm^3 and CD4% ≤22% (CD4 count ≤500 cells/mm^3) in those aged 1–5 years 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.

Table 2. Secondary Prophylaxis of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		• Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 BSA (maximum 25 mg) PO once daily, *plus* leucovorin (when using pyrimethamine), 5 mg PO every 3 days *Option 2* • Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 BSA PO once daily	
Varicella-Zoster Virus Disease (VZV)	N/A	N/A	There is no indication for secondary prophylaxis.

[a] Careful monitoring of drug–drug interactions is critical when using rifabutin or clarithromycin in children on ARVs.

Key: ART = antiretroviral therapy; BSA = body surface area; CD4 = CD4 T lymphocyte; CDC = Centers of Disease Control and Prevention; CNS = central nervous system; CrCl = (estimated) creatinine clearance; GI = gastrointestinal; HBV = hepatitis B virus; HepA = hepatitis A [vaccine]; HSV = herpes simplex virus; IV = intravenous; IVIG = intravenous immunoglobulin; MAC = *Mycobacterium avium* complex; PO = orally; PCP = *Pneumocystis* pneumonia; TE = *Toxoplasma* encephalitis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Updated: April 23, 2026
Reviewed: April 23, 2026

Indication	First Choice	Alternative	Comments/Special Issues
Bacterial Infections Bacterial pneumonia; *S. pneumoniae;* occasionally *S. aureus, H. influenzae,* *P. aeruginosa*	• Amoxicillin 90 mg/kg/dose orally divided every 8 or 12 hours (max 1 g/dose) for outpatient management, *or* • Ampicillin 200–400 mg/kg/day divided every 6 hours (max 2 g/dose) (use higher dose if *S. pneumoniae* MIC ≥4 mcg/mL), *or* • 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)	• Ceftazidime 200–300 mg/kg/day divided every 8 hours IV or IM (max 12 g/day), *or* • Cefepime 50 mg/kg/dose every 8 hours IV or IM (max 2 g/dose)	Alternative treatment should be determined based on local antimicrobial susceptibility patterns or that of the bacterial isolate, if available. For children who are receiving combination ART, have mild or no immunosuppression, and have mild-to-moderate community-acquired pneumonia, oral therapy option would be amoxicillin 45 mg/kg/dose twice daily (maximum dose: 4 g per day). Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (*M. pneumoniae, C. pneumoniae*). Add clindamycin or vancomycin if methicillin-resistant *S. aureus* is suspected (base the choice on local susceptibility patterns). For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (such as ceftazidime or cefepime instead of ceftriaxone). Consider PCP in patients with severe pneumonia or more advanced HIV disease. Evaluate for tuberculosis, cryptococcosis, and endemic fungi as epidemiology suggests.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Candida Infections	Oropharyngeal *Uncomplicated Infection* • Clotrimazole troches, 10-mg troche PO four or five times daily • Nystatin suspension 4–6 mL PO four times daily, *or* one or two 200,000-unit flavored pastilles by mouth four or five times daily *Moderate to Severe OPC* • Fluconazole 3–6 mg/kg/dose PO once daily (maximum dose: 400 mg/day) *Treatment Duration* • 7 to 14 days	Oropharyngeal (Fluconazole-Refractory) • Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily (maximum 200–400 mg/day) for 7–14 days • Posaconazole PowderMix for delayed-release oral suspension in children age ≥2 years and in the weight band for 7–14 days: o *10 kg to <12 kg*: 90 mg PO twice daily on Day 1, followed by 90 mg PO once daily o *12 kg to <17 kg:* 120 mg PO twice daily on Day 1, followed by 120 mg PO once daily o *17 kg to <21 kg:* 150 mg PO twice daily on Day 1, followed by 150 mg PO once daily o *21 kg to <26 kg:* 180 mg PO twice daily on Day 1, followed by 180 mg PO once daily o *26 kg to <36 kg:* 210 mg PO twice daily on Day 1, followed by 210 mg PO once daily o *36–40 kg:* 240 mg PO twice daily on Day 1, followed by 240 mg PO once daily • Posaconazole delayed-release *tablets* in children ≥2 years old and >40 kg body weight: 300 mg PO twice daily on	Itraconazole oral solution **should not** be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease. Central venous catheters should be removed, when feasible, in children with HIV with fungemia. 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). Voriconazole has been used to treat esophageal candidiasis in a small number of immunocompromised children without HIV. Voriconazole Dosing in Pediatric Patients • 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. • Conversion to oral voriconazole should be at 9 mg/kg body weight/dose orally every 12 hours. • Children aged ≥12 years and weighing ≥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). Anidulafungin in Children Aged 2–17 Years

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		Day 1, followed by 300 mg PO once daily for 7–14 days • Posaconazole oral suspension: 6 mg/kg/dose three times daily for 7–14 days • Posaconazole IV: 6 mg/kg/dose (maximum 300 mg) IV twice daily on Day 1, followed by 6 mg/kg/dose (maximum 300 mg) IV once daily for 7–14 days • *Alternative:* Voriconazole: Dosing as per esophageal disease below • *Alternative:* Echinocandins: Dosing as per esophageal disease below • *Alternative:* Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established. • *Alternative:* Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily	• Loading dose of 3 mg/kg body weight/once daily followed by 1.5 mg/kg body weight/once daily (100 mg/day maximum). Fluconazole Dosing Considerations • 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 • *Aged ≥18 Years*: 400 mg/dose once daily (6 mg/kg body weight once daily)
	Esophageal Disease • Fluconazole 6 mg/kg/day PO once on Day 1, then 3–6 mg/kg/dose PO once daily (maximum dose: 12 mg/kg/day, 400 mg/day) *Treatment Duration* • 14–21 days	Esophageal Disease (Intolerance of Oral Therapy) • Fluconazole 6 mg/kg/day IV once on Day 1, then 3–6 mg/kg/dose IV once daily (maximum dose: 12 mg/kg/day, 400 mg/day) for 14–21 days *Echinocandins* • Anidulafungin	N/A

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		○ *Aged 1 Month to 17 Years*: Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV (maximum 100 mg/day) • Caspofungin ○ Infants Aged *<3 Months*: 25 mg/m^2 BSA/dose daily IV ○ *Aged 3 Months to 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 BSA. • Micafungin ○ 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). ○ *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. ○ *Ages ≥4 Months and Weight ≤30 kg:* 3 mg/kg body weight/dose IV daily ○ *Ages ≥4 Months and Weight >30 kg:* 2.5 mg/kg body weight/dose IV daily (maximum dose: 150 mg/day)	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		• Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established. • Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily Esophageal Disease (Fluconazole-Refractory) • Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily • Voriconazole o *Ages 2 Years to <12 Years:* 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. o *Ages 12–14 Years and Weight <50 kg:* 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. o *Ages 12–14 Years and Weight ≥50 kg:* 200 mg PO/IV every 12 hours o *Ages ≥15 Years and Weight <40 kg:* 100 mg PO/IV every 12 hours o *Ages ≥15 Years and Weight ≥40 kg:* 200 mg PO/IV every 12 hours • *Alternative:* Echinocandins: Dosing as above	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		• *Alternative:* Lipid formulation amphotericin B: Dosing as above • *Alternative:* Amphotericin B (deoxycholate): Dosing as above • *Alternative:* Posaconazole: Dosing as above • *Alternative:* Isavuconazonium sulfate IV (372 mg/vial) o *Ages 1 Year to <3 Years and Weight <18 kg:* 15 mg/kg body weight/dose every 8 hours IV loading for six doses (48 hours), followed by 15 mg/kg once daily o *Ages 3 Years to <18 Years and Weight <37 kg:* 10 mg/kg every 8 hours IV loading for six doses (48 hours), followed by 10 mg/kg once daily IV o *Ages 3 Years to <18 Years and Weight ≥37 kg:* 372 mg (total dose) every 8 hours IV loading for six doses (48 hours), followed by 372 mg (total dose) once daily IV • *Alternative:* Isavuconazonium sulfate capsules (74.5 mg/capsule) o *Ages 6 Years to <18 Years and Weight 16 kg to <25 kg:* 149 mg (2 capsules) PO every 8 hours loading for six doses (48 hours), followed by 149 mg (2 capsules) PO once daily o *Ages 6 Years to <18 Years and Weight 18 kg to <25 kg:* 223.5 mg	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		(3 capsules) PO every 8 hours loading for six doses (48 hours), followed by 223.5 mg (3 capsules) PO once daily o *Ages 6 Years to <18 Years and Weight 25 kg to <32 kg:* 298 mg (4 capsules) PO every 8 hours loading for six doses (48 hours), followed by 298 mg (4 capsules) PO once daily o *Ages 6 Years to <18 Years and Weight ≥32 kg:* 372 mg (5 capsules) PO every 8 hours loading for six doses (48 hours), followed by 372 mg (5 capsules) PO once daily *Treatment Duration* • 14–21 days	
	Invasive Disease: Moderately Severe to Severely Ill *Echinocandin Recommended* • Anidulafungin o *Aged 1 Month–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 (maximum 100 mg/day) • Caspofungin: o *Infants Aged <3 Months*: 25 mg/m^2 BSA/dose once daily IV	Invasive Disease • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight IV/PO once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia) o For infants aged ≤3 months and gestational age <30 weeks, maintenance dosing is 9 mg/kg/dose IV/PO daily • Lipid formulations of amphotericin B, 3–5 mg/kg body weight IV once daily	Central venous catheters should be removed, when feasible, in children with HIV with fungemia. The preferred treatment for invasive disease in children with HIV depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). If a child with uncomplicated invasive candidiasis 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 can be considered when the patient is clinically improved, has isolates susceptible to the oral agent, and have negative repeat blood cultures following initiation of antifungal therapy.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	○ *Aged 3 Months–17 Years:* 70 mg/m^2 BSA/day loading dose followed by 50 mg/m^2 once daily (maximum 70 mg). Note: Dosing of caspofungin in children should be based on BSA. • Micafungin: ○ 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). ○ *Neonates*: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. ○ *Infants <15 kg Body Weight:* 5–7 mg/kg/day ○ *Children ≤40 kg Body Weight and Aged 2–8 Years*: 3–4 mg/kg body weight/dose daily IV ○ *Children ≤40 kg Body Weight and Aged 9–17 Years:* 2–3 mg/kg body weight/dose daily ○ *Children >40 kg Body Weight:* 100 mg/dose daily IV *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those	• Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily in the neonatal period • Voriconazole: ○ *Ages 2 Years to <12 Years:* 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours. ○ *Ages 12–14 Years and Weight <50 kg:* 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours. ○ *Ages 12–14 Years and Weight ≥50 kg:* Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. ○ *Ages ≥15 Years and Weight <40 kg:* Load voriconazole 6 mg/kg body	Voriconazole can be used in situations in which mold coverage is also warranted.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	with candidemia, treat until 2 weeks after last positive blood culture. Invasive Candidiasis: Mildly to Moderately Ill *Fluconazole Recommended* • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 600 mg) • For infants aged ≤3 months and gestational age <30 weeks, fluconazole maintenance dosing is 9 mg/kg/dose IV daily. • Avoid fluconazole for *C. krusei* and *C. glabrata.* See dosing for echinocandins above. • Use caution with echinocandins for *C. parapsilosis*. *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture.	weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 100 mg PO every 12 hours. If response is inadequate, may increase to 150 mg PO every 12 hours. o *Ages ≥15 Years and Weight ≥40 kg:* Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. *Treatment Duration* • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture.	
	Invasive Disease: CNS *Neonates* • *Initial:* Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily,	Invasive Disease: CNS *Neonates* • Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily, *or* liposomal	Infected CNS devices should be removed if possible. For patients in whom a ventricular device cannot be removed, amphotericin B deoxycholate could be administered through the device into the ventricle. Intrathecal neonatal doses have ranged from 0.5 mg/day in 2 mL of D5W to 0.6 mg/day in 0.5 mL of

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	or liposomal amphotericin B 5 mg/kg body weight/dose IV daily • *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily *Children* • *Initial:* Liposomal amphotericin B 5 mg/kg body weight/dose IV daily +/- flucytosine 25 mg/kg body weight/dose PO four times daily • *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg) *Treatment Duration* • ≥1 month until all signs, symptoms, and CSF and radiographic abnormalities have resolved	amphotericin B 5 mg/kg body weight/dose IV daily, *and* • Flucytosine 25 mg/kg body weight/dose PO four times daily as salvage therapy *Children* • *Initial:* Amphotericin B deoxycholate 0.7–1 mg/kg body weight/dose IV daily IV daily (maximum 1.5 mg/kg/day) +/- flucytosine 25 mg/kg body weight/dose PO four times daily • *Step-Down (If Fluconazole-Susceptible):* Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg)	D5W (total doses were 0.15 mg to 8.6 mg); doses of 0.125 to 0.25 mg have been administered to children via an Ommaya reservoir. Lipid formulations of amphotericin may not adequately penetrate the kidneys and should only be used with caution in neonates when urinary tract involvement is suspected or confirmed. Fluconazole dosing for CNS candidiasis is unknown but based on dosing for *Candida* invasive disease and maximums from cryptococcal meningitis. In neonates with CNS candidiasis, micafungin 10–15 mg/kg/dose IV daily may be considered as alternative therapy in special circumstances, such as salvage therapy or situations in which toxicity or drug resistance (e.g., *C. glabrata*) preclude the use of the preferred agents.
Coccidioidomycosis	Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease • Liposomal amphotericin B preparation at a dose of 5 mg/kg body weight IV once daily (dose can be increased to as much as	Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease *If Unable to Use Amphotericin B—* • Fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or by mouth once daily	Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful. Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	10 mg/kg body weight IV once daily for life-threatening infections) • Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily until clinical improvement. • Liposomal amphotericin B is the treatment of choice with similar efficacy and fewer adverse events. • 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.	• Treatment is continued for a total of 1 year, followed by secondary prophylaxis.	Some experts initiate an azole during amphotericin B therapy. Others defer initiation of the azole until after amphotericin B is stopped. For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children. Options should be discussed with an expert in the treatment of coccidioidomycosis. Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease. Therapy with amphotericin B results in a more rapid clinical response in severe, non-meningeal disease.
	Mild-to-Moderate Non-Meningeal Coccidioidal Infection • Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily for 6–12 months and clinical improvement	Mild-to-Moderate Non-Meningeal Coccidioidal Infection • Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) per dose IV or PO three times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily thereafter for 6–12 months and clinical improvement • *Age ≥13 Years:* Posaconazole oral (delayed-release tablets), 300 mg twice daily for two doses, followed by 300 mg daily for 6–12 months and clinical improvement	Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful. Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent. For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children. Options should be discussed with an expert in the treatment of coccidioidomycosis. Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm^3 or CD4 percentage <15%.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	Coccidioidal Meningitis • Lifelong fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or PO once daily	Coccidioidal Meningitis • IV liposomal amphotericin B plus intrathecal amphotericin B deoxycholate followed by secondary prophylaxis	For treatment failure, can consider posaconazole, isavuconazole, or voriconazole. Chronic suppressive therapy (secondary prophylaxis) with fluconazole is continued lifelong for meningeal disease. Options for treatment and secondary prophylaxis should be discussed with an expert in the treatment of coccidioidomycosis in children.
COVID-19	Non-hospitalized Children at High Risk of Progression to Severe COVID-19 *Aged ≥28 Days to <12 Years* • Remdesivir (Veklury) o ≥3 to <40 kg: Lyophilized powder only; IV loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose once daily on Days 2 and 3 o ≥40 kg: Injection solution or lyophilized powder; IV loading dose: 200 mg on Day 1, followed by 100 mg once daily on Days 2 and 3 *Aged ≥12 Years and ≥40 kg* • Nirmatrelvir 300 mg and ritonavir 100 mg, administered together (Paxlovid), twice daily for 5 days Hospitalized Children • Remdesivir (Veklury)	Non-hospitalized Children at High Risk of Progression to Severe COVID-19 *Aged ≥28 Days to <12 Years* • N/A *Aged ≥12 Years* • Remdesivir (Veklury) o ≥3 to <40 kg: Lyophilized powder only, IV: loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose once daily on Days 2 and 3	Remdesivir is administered intravenously. When given to non-hospitalized patients, duration is for 3 days. When given to hospitalized patients, duration is generally 5 days or until hospital discharge, whichever is first, but may extend to up to 10 days based on clinical response. Remdesivir should be started within 7 days of symptom onset but could be considered if presenting with >7 days of symptoms in children with severe immunosuppression. Ritonavir-boosted nirmatrelvir is an oral PI that may be administered with other ARVs, including those that contain ritonavir or cobicistat, without any interruption or modification to the usual ART. However, there is potential for significant drug–drug interactions with other medications, requiring dose or frequency adjustment or avoidance. Consult a drug interactions database, such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance. Ritonavir-boosted nirmatrelvir should be started within 5 days of symptom onset. Renal and hepatic function should be evaluated prior to initiating ritonavir-boosted nirmatrelvir, and doses should be adjusted if needed. Dexamethasone has potential for drug–drug interactions, including with NNRTIs. Providers should

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	○ ≥3 to <40 kg: Lyophilized powder only; IV loading dose: 5 mg/kg/dose on Day 1, followed by 2.5 mg/kg/dose once daily on Days 2 through 5 ○ ≥40 kg: Injection solution or lyophilized powder; IV loading dose: 200 mg on Day 1, followed by 100 mg once daily on Days 2 through 5 • Dexamethasone 0.15 mg/kg (with a maximum dose of 6 mg), oral or IV, once daily for up to 10 days		consult a drug interactions resource, such as the University of Liverpool COVID-19 Drug–Drug Interaction website, for further guidance. Alternative corticosteroids, such as hydrocortisone or methylprednisolone, may be considered if dexamethasone is not available or if alternative corticosteroids are being administered for another indication.
Cryptococcosis	CNS Disease *Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)* • 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 *Consolidation Therapy (Followed by Secondary Prophylaxis)* • 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 *Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)* • If Flucytosine Not Tolerated or Unavailable— ○ 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	In patients with meningitis, CSF culture should be negative prior to initiating consolidation therapy. 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. Liposomal amphotericin and amphotericin B lipid complex are especially useful for children with renal insufficiency or infusion-related toxicity to amphotericin B deoxycholate. Liposomal amphotericin and amphotericin B lipid complex are **significantly** more expensive than amphotericin B deoxycholate. Liquid preparation of itraconazole (if tolerated) is preferable to tablet formulation because of better

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		for fluconazole with use of such combination therapy. • If Amphotericin B-Based Therapy Not Tolerated— 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 • Consolidation Therapy (Followed by Secondary Prophylaxis) 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.	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. Serum itraconazole concentrations should be monitored to optimize drug dosing. Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake, or impair its renal excretion, or both. Flucytosine dose should be adjusted to keep 2-hour post-dose drug levels at 40–60 µg/mL. Oral acetazolamide should not be used for reduction of ICP in cryptococcal meningitis. Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis. Secondary prophylaxis is recommended following completion of initial therapy (induction plus consolidation)—drugs and dosing listed above. [a] Duration of therapy for non-CNS disease depends on site and severity of infection and clinical response
	Localized Disease, Including Isolated Pulmonary Disease (CNS Not Involved)[a] • 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] • Amphotericin B, 0.7–1.0 mg/kg body weight, *or* • Amphotericin liposomal 3–5 mg/kg body weight, *or*	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		• Amphotericin lipid complex, 5 mg/kg body weight IV once daily	
	Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[a] • Amphotericin B 0.7–1.0 mg/kg body weight, *or* • Liposomal amphotericin, 3–5 mg/kg body weight, *or* • Amphotericin B lipid complex 5 mg/kg body weight IV once daily (± flucytosine)	Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease[a] • 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	
Cryptosporidiosis	Effective ART • 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. Nitazoxanide • 1–3 years of age: Nitazoxanide (20 mg/mL oral solution) 100 mg orally twice daily with food • 4–11 years of age: Nitazoxanide (20 mg/mL oral solution) 200 mg orally twice daily with food • ≥12 years of age: Nitazoxanide tablet 500 mg orally twice daily with food *Treatment Duration* • 3–14 days	Supportive Care • Hydration, correct electrolyte abnormalities, nutritional support Antimotility agents (such as loperamide) should be used with caution in young children.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Cytomegalovirus Infection (CMV)	Symptomatic Congenital Infection With Neurologic Involvement • 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		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. Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children. 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. 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.
	Disseminated Disease and Retinitis *Induction Therapy* • 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) *Chronic Maintenance Therapy* • Ganciclovir 5 mg/kg body weight once daily for 5–7 days	Disseminated Disease and Retinitis *Induction Therapy* • 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 *Chronic Maintenance Therapy* • Foscarnet 90–120 mg/kg body weight IV once daily *Alternative Therapy for Retinitis (Followed by Chronic Maintenance Therapy; See Cytomegalovirus Row in Secondary Prophylaxis Table)* • Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above). 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
		• 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. • 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 *Induction Therapy* • 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 *Chronic Maintenance Therapy* • 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
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 • Nitazoxanide o *1–3 years*: 100 mg by mouth every 12 hours with food for 3 days o *4–11 years*: 200 mg by mouth every 12 hours with food for 3 days o ≥*12 years*: 500 mg by mouth every 12 hours with food for 3 days 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. 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. Supportive Care • Hydration • Correction of electrolyte abnormalities • Nutritional support Antimotility agents (e.g., loperamide) should be used with caution in young children.
Hepatitis B Virus Infection (HBV)	Treatment of Both HIV and HBV Required *Child Not Already Receiving 3TC or FTC* • 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive ART regimen • For children aged ≥2 years, TAF as part of ART regimen with 3TC or FTC	Alternative for 3TC: FTC 6 mg/kg bodyweight (maximum 200 mg) once daily	Indications for Treatment Include— • Detectable serum HBV DNA, irrespective of HBeAg status, for >6 months; *and* • Persistent (≥6 months) elevation of serum transaminases (≥ twice the upper limit of normal); *or* • Evidence of chronic hepatitis on liver biopsy Choice of HBV treatment options for children with HIV/HBV infection depends upon whether concurrent HIV treatment is warranted.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• For children ≥14 kg to <25 kg, FTC 120 mg/TAF 15 mg FDC once daily • For children ≥25 kg, FTC 200 mg/TAF 25 mg FDC once daily, or 3TC 300 mg plus 25 mg TAF daily • Note: For children weighing <35 kg, FTC/TAF combination should not be used with protease inhibitors for HIV therapy *Child Already Receiving ART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance* • For children aged ≥2 years, include TDF or TAF as part of ART regimen with 3TC or FTC o For children aged <12 years, TDF 8 mg/kg body weight per dose once daily (maximum dose 300mg) o For children aged ≥12 years, TAF 25 mg once daily • For children aged ≥12 years, add entecavir 0.5 mg by mouth once daily in addition to ART regimen		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. TAF is approved for use in treatment of HIV infection in children aged ≥2 years but is not approved for treatment of HBV infection in children aged <12 years. It should only be used for HBV in children with HIV/HBV coinfection as part of an ART regimen. Entecavir is approved for use in children without HIV ≥2 years of age for treatment of chronic HBV. It should only be used for HBV in children with HIV/HBV coinfection who also receive an HIV-suppressive ART regimen but cannot use or access tenofovir. IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6-12 weeks of ART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS. In children receiving TDF or TAF 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 >12 months after HBeAg seroconversion and can be closely monitored on discontinuation. If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening.
Hepatitis C Virus Infection (HCV)	For detailed dosing recommendations for HCV antiviral therapy in children	For detailed dosing recommendations for HCV antiviral therapy in children and	The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	and adolescents, refer to the section on HCV in Children.	adolescents, refer to the section on HCV in Children.	Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C virus (HCV) management. See the AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C for more details. For more information on other important considerations in the management of HCV in children and adolescents with HIV—such as drug–drug interactions, alternate therapies, dose adjustment, and extra monitoring—refer to the section on Patients With HIV/HCV Coinfection.
Herpes Simplex Virus Infection (HSV)	Neonatal CNS or Disseminated Disease • Acyclovir 20 mg/kg body weight IV/dose every 8 hours for ≥21 days Neonatal Skin, Eye, or Mouth Disease • Acyclovir 20 mg/kg body weight IV/dose every 8 hours for 14 days CNS or Disseminated Disease in Children Outside the Neonatal Period • 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		For Neonatal CNS Disease— • 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.
	Moderate to Severe Symptomatic Gingivostomatitis	• Valacyclovir is approved for immunocompetent adults and adolescents with first-episode	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• 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. Mild Symptomatic Gingivostomatitis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth four times a day for 7–10 days Recurrent Herpes Labialis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth four times a day for 5 days For First-Episode Genital Herpes (Adults and Adolescents)— • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth three times a day for 7–10 days	mucocutaneous HSV at a dose of 1 g/dose by mouth twice daily 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. • Recurrent genital HSV can be treated with valacyclovir 500 mg twice daily for 3 days or 1 g by mouth daily for 5 days. • Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth twice daily for 1 day. • Famciclovir is approved to treat primary genital HSV in immunocompetent adults at a dose of 250 mg/dose by mouth three times daily for 7–10 days. • Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth twice daily at a 12-hour interval for 2 doses. • 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 twice daily for 7 days.	
	Recurrent Genital Herpes (Adults and Adolescents)		Alternative and Short-Course Therapy in Immunocompromised Adults With Recurrent Genital Herpes

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth three times daily for 5 days Children With HSV Keratoconjunctivitis • 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. Children With ARN • 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 three times daily for 4–6 weeks • As an alternative, oral acyclovir 20 mg/kg body weight/dose four times daily for 4–6 weeks after IV acyclovir for 10–14 days		• Acyclovir 800 mg per dose by mouth twice daily for 5 days • Acyclovir 800 mg per dose by mouth three times daily for 2 days 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.
		Acyclovir-Resistant HSV Infection • 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	Acute Primary Pulmonary Histoplasmosis	Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• 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.	• Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily	capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules. 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. 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. High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered. Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy. Amphotericin B deoxycholate is better tolerated in children than in adults. Liposomal amphotericin B is preferred for treatment of parenchymal cerebral lesions.
	Mild Disseminated Disease • 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 • 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	
	Moderately Severe to Severe Disseminated Disease *Acute Therapy (Minimum 2-Week Induction, Longer if Clinical Improvement Is Delayed, Followed by Consolidation Therapy):* • Liposomal amphotericin B 3–5 mg/kg body weight, IV once daily (preferred)	Moderately Severe to Severe Disseminated Disease • 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.	

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) *Consolidation Therapy (Followed by Chronic Suppressive Therapy):* • 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	• Liposomal amphotericin B 3–5 mg/kg body weight IV once daily (preferred) for 4–6 weeks • Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) for 4–6 weeks	
	Central Nervous System Infection *Acute Therapy (4–6 Weeks, Followed by Consolidation Therapy)* • Liposomal amphotericin B, 5 mg/kg body weight IV once daily (AII) *Consolidation Therapy (Followed by Chronic Suppressive Therapy)* • 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		

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
Human Papillomavirus Disease (HPV)	Monitoring for spontaneous resolution is a reasonable option; 30% resolve spontaneously within 6 months and 90% within several years. Patient- or Parent-Applied Treatment Options • Imiquimod (3.75% or 5%) cream applied topically at night and washed off in the morning for 3 nonconsecutive nights a week for up to 16 weeks (BII) • Podofilox (0.5%) solution/gel applied topically two times daily for 3 consecutive days a week. Withhold treatment for 4 days and repeat the cycle weekly up to four times (BIII). • Sinecatechins (15%) ointment applied three times daily for up to 16 weeks, until warts are cleared completely and not visible (BIII) Provider-Applied Treatment Options • TCA (80% to 90%) applied topically weekly for up to 3 to 6 weeks (BIII). • Cryotherapy with liquid nitrogen or cryoprobe applied every 1–2 weeks up to four times (BIII). • Surgical removal either by tangential excision, tangential shave excision, curettage, or electrosurgery (BIII)	Patient- or Parent-Applied Treatment Options • Cidofovir topical gel (1%) is an experimental therapy studied in adults with HIV that is commercially available through compounding pharmacies and has very limited use in children; systemic absorption can occur with potential for renal toxicity (CIII). Provider-Applied Treatment Options • Intralesional IFN-α and 5-FU/ epinephrine gel implant are generally not recommended because of high cost, difficult administration, potential for systemic side effects, and lack of testing in children (CIII). Note: These alternative therapies should include consultation with infectious disease and dermatological specialists.	When choosing treatment options, parent and child comfort in application should be considered. Children have a low pain threshold and, generally, sensitive skin. Adequate topical anesthetics to the genital area should be given before caustic modalities are applied. For young children, these approaches are poorly tolerated due treatment-related and postoperative pain, and as a result may require general anesthesia. Therefore, these should be mainly reserved for children with extensive lesions. Many of these agents are contraindicated in pregnancy and have potential teratogenic effect. When treatment options are considered, the potential for pregnancy should be discussed and proper precautions during pregnancy explained.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
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 Second-Line Alternatives • Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth twice daily for 7 days • Nitazoxanide (see doses below) for 3 consecutive days *Children Aged 1 Year–3 Years* • Nitazoxanide 100 mg by mouth every 12 hours *Children Aged 4 Years–11 Years* • Nitazoxanide 200 mg by mouth every 12 hours *Adolescents Aged ≥12 Years and Adults* • 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. The optimal duration of treatment with pyrimethamine has not been established. 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.
Malaria	Uncomplicated *P. Falciparum* or Unknown Malaria Species, From Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region • 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. Before primaquine is given, G6PD status must be verified. Primaquine may be given in combination with chloroquine if the G6PD status is known and

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	o 5–8 kg; 2 pediatric tablets for 3 days; o 9–10 kg; 3 pediatric tablets for 3 days; o 11–20 kg; 4 pediatric tablets or 1 adult tablet for 3 days; o 21–30 kg; 2 adult tablets for 3 days; o 31–40 kg; 3 adult tablets for 3 days; o >40 kg; 4 adult tablets for 3 days Uncomplicated *P. Falciparum* OR Unknown Malaria Species from Chloroquine-Sensitive Region (See Comments for Link to Resistance Map) • 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) *P. vivax, P. ovale, P. malariae, P. knowlesi* (All Areas Except Papua New Guinea, Indonesia; See Comments)		negative, otherwise give after chloroquine (when G6PD status is available) 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 For sensitive and resistant malaria map: https://www.cdc.gov/malaria/travelers/country_table/a.html 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: • Atovaquone-proguanil plus primaquine phosphate • Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate. This regimen cannot be used in children aged <8 years. • 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
	Initial Therapy *(Followed by Anti-Relapse Therapy for* P. ovale *and* P. vivax*):* • 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) *Anti-Relapse Therapy for* P. ovale *and* P. vivax*:* • Primaquine 0.5 mg base/kg body weight (max 30 mg base) by mouth once daily for 14 days Uncomplicated *P. falciparum* or Unknown Malaria Species from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region • 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 • Quinine sulfate 10 mg/kg body weight (maximum 650 mg) per dose		

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	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. • 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. o 5 to <15 kg; 1 tablet per dose o 15 to <25 kg; 2 tablets per dose o 25 to <35 kg; 3 tablets per dose 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) *Plus One of the Following:*	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,

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• 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, *or* • Clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours for 7 days, *or* • 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 • Artesunate 2.4 mg/kg body weight IV bolus at 0, 12, 24, and 48 hours *Plus One of the Following:* • Doxycycline (treatment dosing as above), or Atovaquone-proguanil (treatment dosing as above), *or* • 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* • Clindamycin (dosing as above)		and hypotension can result from the use of this drug at treatment doses. Investigational New Drug: 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. Quinidine gluconate: 10 mg = 6.25 mg quinidine base. 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. 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. *Drug Interactions* • Avoid co-administration of quinidine with ritonavir • Use quinidine with caution with other protease inhibitors.
Microsporidiosis	Effective ART	N/A	Supportive care (e.g., hydration, correction of electrolyte abnormalities, nutritional support)

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• Immune reconstitution may lead to microbiologic and clinical response. For Disseminated (Not Ocular) and Intestinal 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 (in addition to ART) *Treatment Duration* • 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 For *E. bieneusi* or *V. corneae* Infections— • Fumagillin (where available) adult dose 20 mg by mouth 3 times daily, *or* • 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) For Ocular Infection— • Topical fumagillin bicyclohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70		Fumagillin for systemic use is unavailable in the United States and data on dosing in children are unavailable. Consultation with an expert is recommended.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	μg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops four times daily (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) *Treatment Duration* • 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.		
Mycobacterium avium Complex (MAC)	**Initial Treatment (≥2** Drugs): • Clarithromycin[a] 7.5–15 mg/kg (maximum 500 mg/dose) PO twice daily, *plus* • Ethambutol 15–25 mg/kg (maximum 2.5 g/day) PO once daily followed by chronic suppressive therapy *If Experiencing Severe Disease (Extensive End Organ Involvement, Prolonged Symptoms, Slow Response to Therapy)* • Add rifabutin[a] 10–20 mg/kg (maximum 300 mg/day) PO once daily	If Intolerant to Clarithromycin • Azithromycin 10–12 mg/kg (maximum 500 mg/day) PO once daily, plus ethambutol For Children With Severe Symptoms or Disseminated Disease Who Need a Rifabutin Alternative or a Fourth Drug to Supplement a Macrolide/ Ethambutol/Rifabutin Regimen • Amikacin[b] 15–30 mg/kg (maximum 1.5 g/day) IV in one or two divided doses. Therapeutic drug monitoring (peak and trough levels) is required, *or* • Linezolid 10 mg/kg/dose PO every 8 hours for age 1 month to <12 years	Susceptibility testing is recommended prior to treatment initiation. Combination therapy with a minimum of two drugs is recommended for ≥12 months. Careful monitoring for drug–drug interactions is advised. Clofazimine is associated with increased mortality in adults with HIV and should not be used. Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination. Fluoroquinolones (e.g., ciprofloxacin and moxifloxacin) are used with caution in children aged

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		(maximum 600 mg/dose) and 10 mg/kg/dose PO every 12 hours (maximum 600 mg) for age ≥12 years, *or* • Moxifloxacin 7.5–10 mg/kg (maximum dose 400 mg daily) PO once daily, *or* • Levofloxacin 15-20 mg/kg/dose PO once daily (maximum dose 750 mg), *or* • Ciprofloxacin 10–15 mg/kg (maximum 1.5 g/day) PO twice daily, *or* • Bedaquiline for children aged ≥5 years weighing ≥15 kg (based on MDR-TB regimens): o *Weeks 1–2:* 400 mg once daily o *Weeks 3–24:* 200 mg three times weekly • For therapy beyond 24 weeks, consider consultation with a pediatric infectious disease/HIV expert.	<18 years because of concerns regarding potential effects on cartilage; use in children aged <18 years requires an assessment of potential risks and benefits. Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. Limited data for bedaquiline in adults with NTM.
Mycobacterium tuberculosis	Intrathoracic Disease *Drug-Susceptible TB* • Intensive Phase (2 Months) o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily, plus	Alternative for Rifampin • Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if three times a week) • Discuss with an expert. Alternative Continuation Phase With Three Times Weekly Dosing (4 Months) *If Good Adherence and Treatment Response*	Treatment for TB disease should always be provided by DOT. If ART-naive, start TB therapy immediately and initiate ART within 2–8 weeks. If already on ART, review regimen to minimize potential toxicities and drug interactions; start TB treatment immediately. Potential drug toxicity and interactions should be reviewed at every visit. Drug interactions with ART

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	○ Pyrazinamide 30–40 mg/kg body weight (maximum 2 g/day) by mouth once daily, plus ○ Ethambutol 15–25 mg/kg body weight (maximum 1 g/day) by mouth once daily ○ In children with minimal disease with fully drug-susceptible TB, some experts recommend a three-drug intensive phase regimen excluding ethambutol. • Continuation Phase (4 Months) ○ Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus ○ Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily Extrathoracic Disease Note: Depends on disease entity • Lymph node TB—treat as minimal intrathoracic disease • Bone or joint disease—consider extending the continuation phase to 10 months (for total duration of therapy of 12 months). TB Meningitis • As an alternative to ethambutol, streptomycin 20–40 mg/kg body weight (maximum 1 g/day) IM once daily. During intensive phase,	• Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth three times per week, plus • Rifampin 15–20 mg/kg body weight (maximum 600 mg/day) three times per week • 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)	should be considered for all rifamycin-containing alternatives. Adjunctive Treatment • Co-trimoxazole prophylaxis • 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 girls and women. • 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. Second-Line Drug Doses • 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.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	consider ethionamide, 15–20 mg/kg body weight by mouth (maximum 1 g/day), initially divided into two doses until well tolerated. • 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. • Consider extending the continuation phase to 10 months (for a total duration of therapy of 12 months). • Discuss with an expert. Drug-Resistant TB • 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 15–20 mg/kg/day (TMP component) in divided doses every 6–8 hours IV or PO for 21 days (followed by secondary prophylaxis dosing)	If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy *Pentamidine* • 4 mg/kg/dose IV/IM once daily is the first-choice alternative regimen for severe disease. • Note: Close electrolyte and glucose monitoring required. Pentamidine can be changed to atovaquone after 7–10 days IV therapy. Atovaquone can be	After acute pneumonitis resolved in mild-to-moderate PCP, IV TMP-SMX can be transitioned to oral formulations. For oral administration, total daily dose of TMP-SMX can also be administered in three divided doses (every 8 hours). The following regimens have been used in adults, but data in children are limited: • Dapsone 2 mg/kg/dose PO once daily (maximum 100 mg/day) plus trimethoprim 5 mg/kg/dose PO every 8 hours

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
		considered for initial therapy in mild-to-moderate disease. *Atovaquone* • Daily Dosing o *Children Aged 1–3 Months and >24 Months to 12 Years:* 30–40 mg/kg/dose PO once daily with food o *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food • Twice-Daily Dosing o *Children Aged ≥13 Years:* 750 mg/dose PO twice daily o 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/dose PO twice daily with food ▪ *Children Aged 4–24 Months:* 22.5 mg/kg/dose PO twice daily with food	• Primaquine base 0.3 mg/kg/dose PO once daily (maximum 30 mg/day) plus clindamycin 10mg/kg/dose IV or PO (maximum 600 mg/dose given IV and 300–450 mg/dose given orally) every 6 hours Chronic suppressive therapy (secondary prophylaxis) with TMP-SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis). Corticosteroids Adjunctive Therapy *Indication* • PaO_2 <70 mmHg at room air or alveolar-arterial oxygen gradient ≥35 mmHg *Prednisone Dose* • Days 1–5: 1 mg/kg/dose PO twice daily, then • Days 6–10: 0.5–1 mg/kg/dose PO twice daily, then • Days 11–21: 0.5 mg/kg/dose PO once daily. *Alternative Corticosteroid Regimens* • Adult Dosage of Prednisone o Days 1–5: 40 mg/dose PO twice daily, then o Days 6–10: 40 mg/dose PO once daily, then o Days 11–21: 20 mg/dose PO once daily • Methylprednisolone IV o Days 1–7: 1 mg/kg/dose every 6 hours, then o Days 8–9: 1 mg/kg/dose twice daily, then

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
			o Days 10–11: 0.5 mg/kg/dose twice daily, then o Days 12–16: 1 mg/kg/dose once daily
Syphilis	Congenital *Proven or Highly Probable Disease* • Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose IV every 12 hours for the first 7 days of life, and then every 8 hours for 10 days • 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 *Possible Disease* • 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 *Proven or Highly Probable Disease (Less Desirable if CNS Involvement)* • Procaine penicillin G 50,000 units/kg body weight IM once daily for 10 days *Possible Disease* • 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. 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. In the setting of maternal and possible infant HIV infection, the more conservative choices among scenario-specific treatment options may be preferable. Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	Acquired *Early Stage (Primary, Secondary, Early Latent)* • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM for 1 dose *Late Latent* • Benzathine penicillin 50,000 units/kg body weight (maximum 2.4 million units) IM once weekly for 3 doses *Neurosyphilis (Including Ocular)* • 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
Toxoplasmosis	Congenital Toxoplasmosis • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 mg PO or IM three times weekly, *plus* • Sulfadiazine 50 mg/kg body weight PO twice daily *Treatment Duration* • 12 months Acquired Toxoplasmosis *Acute Induction Therapy (Followed by Chronic Suppressive Therapy)* • Pyrimethamine loading dose of 1 mg/kg body weight (maximum 50 mg) PO twice daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) PO once daily, *plus* • Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) PO per dose four times daily, *plus* • Leucovorin 10–20 mg PO once daily, continued for one week after stopping pyrimethamine *Treatment Duration (Followed by Chronic Suppressive Therapy)*:	For Sulfonamide-Intolerant Patients: • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 PO or IM three times weekly, *plus* • Clindamycin 5–7.5 mg/kg body weight PO or IV (maximum 600 mg/dose) per dose four times daily	Congenital Toxoplasmosis • For infants born mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of treatment during pregnancy. Acquired Toxoplasmosis • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less-than-daily dosing. • The following regimens are used in adults but have not been studied in children: o TMP-SMX 5/25 mg/kg body weight per dose IV or PO given twice daily as an alternative to pyrimethamine-sulfadiazine o Atovaquone 1,500 PO twice daily administered— ▪ with pyrimethamine and leucovorin, *or* ▪ with sulfadiazine, *or* ▪ alone, for those with pyrimethamine and sulfadiazine intolerance o Azithromycin 900–1,200 mg daily (corresponding to 20 mg/kg daily, maximum 1,000 mg in children) administered with pyrimethamine-leucovorin • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or when focal lesions with significant mass effects are

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)		present, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to people with a history of seizures and continued through the acute treatment but should not be used prophylactically. • Sulfadiazine may be given as two to four equal doses per day as long as the total daily dose is 85–120 mg/kg body weight. • Consider screening for G6PD deficiency before starting sulfadiazine or TMP-SMX in people from regions with high prevalence of severe G6PD deficiency.
Varicella-Zoster Virus Disease (VZV)	Varicella *Children With Severe Immunosuppression (HIV Stage 3) or Severe Varicella Disease (see* Treating Disease *in text)* • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours for at least 7 days and until no new lesions appear for 48 hours *Children With No or Moderate Immunosuppression (HIV Stage 1 and 2) and Mild Varicella Disease* • If age ≥3 months: o Valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7–14 days	*Children Unresponsive to Acyclovir When Resistance Is Suspected* • Foscarnet: 120–180 mg/kg/day IV divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours *Children in Whom IV Acyclovir Is Indicated, in the Setting of a National Shortage of IV Acyclovir* • Foscarnet: 120–180 mg/kg/day IV divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours, *or* • Ganciclovir 5 mg/kg/dose IV every 12 hours for at least 7 days and until no new lesions appear for 48 hours	For children aged <2 years, the dose of IV acyclovir is 10 mg/kg/dose every 8 hours. For children aged ≥2 years, some health care providers administer the same dose or base the dose on body surface area (500 mg/m^2/dose IV every 8 hours). When children treated with IV acyclovir show signs of clinical improvement with no new lesions for 48 hours, completion of antiviral therapy with an oral agent may be considered. Renal dose adjustments listed below are only applicable for IV acyclovir: • CrCl >50 mL/minute/1.73 m^2: No dose adjustment necessary • CrCl 25 to 50 mL/minute/1.73 m^2: Administer the usual recommended dose every 12 hours

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	• If age <3 months OR unable to obtain valacyclovir suspension: o Acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily for 7–14 days		• CrCl 10 to <25 mL/minute/1.73 m^2: Administer the usual recommended dose every 24 hours • CrCl <10 mL/minute/1.73 m^2: Administer 50% of the usual recommended dose every 24 hours (e.g., if the usual recommended dose is 10 mg/kg/dose every 8 hours, then administer 5 mg/kg/dose every 24 hours) • Intermittent hemodialysis: 5 mg/kg/dose IV every 24 hours; administer after hemodialysis on dialysis days • Peritoneal dialysis: 5 mg/kg/dose IV every 24 hours; no supplemental dose needed • Continuous renal replacement therapy: 10 mg/kg/dose IV every 12 hours For patients with renal impairment on PO acyclovir, the Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for adults with renal impairment. In children receiving acyclovir, it is important to maintain adequate hydration to avoid crystallization of the drug in the renal tubules. Valacyclovir doses should be adjusted for renal impairment; however, no formal pediatric renal dosing guidelines exist for valacyclovir. The Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for adults with renal impairment (see package insert). There is no pediatric preparation of valacyclovir, although 500 mg caplets can be extemporaneously compounded to make a suspension.

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Indication	First Choice	Alternative	Comments/Special Issues
			For patients with renal impairment on IV foscarnet, the Panel recommends consultation with a pediatric pharmacist and extrapolation of dose adjustments used for management of cytomegalovirus.
	Herpes Zoster *Children With Severe Immunosuppression (HIV Stage 3), Trigeminal or Sacral Nerve Involvement, Visceral Involvement, Extensive Multidermatomal, or Disseminated HZ* • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours for 10–14 days *Children With No or Moderate Immunosuppression (HIV Stage 1 and 2) and Uncomplicated HZ* • If age ≥3 months: o Valacyclovir 20 mg/kg/dose (max: 1,000 mg/dose) PO three times daily for 7–14 days If age <3 months or unable to obtain valacyclovir suspension: • Acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily for 7–14 days	*Children Unresponsive to Acyclovir When Resistance Is Suspected* • Foscarnet IV: 120–180 mg/kg/day divided every 8–12 hours for at least 7 days and until no new lesions appear for 48 hours Famciclovir is approved for use in adults (age ≥18 years) with HZ at a dose of 500 mg/dose PO three times daily for 7–14 days; however, data are insufficient to support the use of famciclovir for HZ in children with HIV.	For most cases, oral treatment (as opposed to IV) for HZ is considered safe because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. For renal dose adjustment and other administration considerations with acyclovir, valacyclovir, and foscarnet, see Varicella above.

Table 3. Treatment of Opportunistic Infections in Children With and Exposed to HIV—Summary of Recommendations

Indication	First Choice	Alternative	Comments/Special Issues
	Children With Progressive Outer Retinal Necrosis • Acyclovir 10 mg/kg/dose or 500 mg/m^2/dose IV every 8 hours OR ganciclovir 5 mg/kg/dose IV every 12 hours, *plus* • Foscarnet 90 mg/kg/dose IV every 12 hours, *plus* • Ganciclovir 2 mg/0.05 mL intravitreal twice weekly AND/OR foscarnet 1.2 mg/0.05 mL intravitreal twice weekly *Children With Acute Retinal Necrosis* • Acyclovir 10 mg/kg/dose or 500 mg/m2/dose IV every 8 hours for 10–14 days, **followed by** valacyclovir 20 mg/kg/dose (max: 1,000 g/dose) PO three times daily for 4–6 weeks OR acyclovir 20 mg/kg/dose (max: 800 mg/dose) PO four times daily 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. Optimal management of progressive outer retinal necrosis has not been defined.

[a] Careful monitoring of drug–drug interactions is critical when using rifabutin or clarithromycin in children on ARVs.

[b] Amikacin levels for therapeutic drug monitoring: peak (C_{max}) 30–40 mg/L and trough (C_{min}) <5 mg/L for once daily dosing; C_{max} 65–80 mg/L for thrice weekly dosing

Key: 3TC = lamivudine; 5-FU = 5-fluorouracil; AAP = American Academy of Pediatrics; ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; BSA = body surface area; CBC = complete blood count; CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; D5W = 5% dextrose in water; DOT = directly observed therapy; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; HZ = herpes zoster; ICP = intracranial pressure; IFN-α = interferon-alfa; IGRA = interferon-gamma release assay; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LIP = lymphocytic interstitial pneumonia; MIC = minimum inhibitory concentration; NNRTI = non-nucleoside reverse transcriptase inhibitors; OPC = oropharyngeal; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PI = protease inhibitor; PK = pharmacokinetic; PO = orally; TAF = tenofovir alafenamide; TB = tuberculosis; TCA = trichloroacetic acid; TDF = tenofovir disproxil fumarate; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole; WHO = World Health Organization

Table 4. Common Drugs Used for Treatment of Opportunistic Infections in Children With HIV: Preparations and Major Toxicities

Updated: June 05, 2025
Reviewed: June 05, 2025

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Acyclovir	Oral Suspension • 40 mg/mL Capsules • 200 mg Tablets • 400 mg • 800 mg IV • 500 mg	More Frequent • Phlebitis (at injection site when given IV) Less Frequent • Acute renal failure (parenteral use, more common with rapid infusion) Rare *Parenteral Form Only* • Encephalopathy • Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia, hemolysis) • Crystalluria, hematuria • Disseminated intravascular coagulation • Hypotension • Neuropsychiatric toxicity (with high doses)	More Frequent • GI disturbances (anorexia, diarrhea, nausea, vomiting) • Headache, lightheadedness • Malaise Less Frequent (More Common in Adults Than Children) • Agitation • Alopecia • Dizziness • Myalgia, paresthesia • Somnolence	Requires dose adjustment in children with renal impairment. Avoid other nephrotoxic drugs. To avoid renal tubular damage related to crystalluria, administer IV preparation by slow IV infusion over at least 1 hour at a final concentration not to exceed 7 mg/mL. This must be accompanied by adequate hydration. Use caution with IV preparation in children with underlying neurological conditions, serious hepatic or electrolyte abnormalities, or substantial hypoxia.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		Parenteral and Oral Forms • Rash (urticarial, exfoliative skin disorders including SJS) • Anaphylaxis • Seizures • Elevated ALTs and ASTs • Fever • Hallucinations • Leukopenia • Lymphadenopathy • Peripheral edema • Visual abnormalities		
Albendazole	Tablet • 200 mg	More Frequent • Abnormal ALTs and ASTs Less Frequent • Hypersensitivity (rash, pruritus) • Neutropenia (with high doses) Rare • Pancytopenia	Less Frequent • CNS effects (dizziness, headache) • GI disturbances (abdominal pain, diarrhea, nausea, vomiting) Rare • Alopecia	Should be given with food. Recommend giving with a high-fat meal to increase absorption. May crush or chew tablets and give with water. Monitor CBC and LFTs prior to each cycle and every 2 weeks during therapy. Pregnancy tests may be administered.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Amikacin	IV • 500 mg • 1,000 mg	More Frequent • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Ototoxicity, both auditory and vestibular Less Frequent • Hypersensitivity (skin rash, redness, or swelling) Rare • Neuromuscular blockade	N/A	Must be infused over 30 to 60 minutes to avoid neuromuscular blockade. Requires dose adjustment in children with impaired renal function. Should monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy. TDM indicated. Use with caution in children on ECMO; PK may be altered. Dose adjustment with close monitoring necessary.
Amphotericin B Deoxycholate	IV • 50 mg	More Frequent • Infusion-related reactions (fever/chills, hypotension, anaphylaxis) • Anemia • Hypokalemia • Renal function impairment • Thrombophlebitis (at injection site) Less Frequent or Rare • Blurred or double vision • Cardiac arrhythmias, usually with rapid infusions	• GI disturbance (nausea, vomiting, diarrhea, abdominal pain) • Headache	Monitor BUN, Cr, CBC, electrolytes, LFTs, fluid status and input/output, signs of hypokalemia. Infuse over 1 to 2 hours; in children with azotemia, hyperkalemia, or getting doses >1 mg/kg, infuse over 3 to 6 hours. Requires dose reduction in children with impaired renal function.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		• Hypersensitivity (rash) • Leukopenia • Polyneuropathy • Seizures • Thrombocytopenia		Avoid other nephrotoxic drugs, when possible, because nephrotoxicity is exacerbated with concomitant use of other nephrotoxic drugs; permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity may be ameliorated by hydration with 0.9% saline IV over 30 minutes prior to the amphotericin B infusion. Infusion-related reactions are less frequent in children than adults; the onset is usually 1 to 3 hours after infusion, duration <1 hour; frequency decreases over time. Addition of heparin to infusion solution may reduce phlebitis. Flush line with dextrose; NS may cause precipitate. Pre-treatment with acetaminophen and/or diphenhydramine may alleviate febrile reactions.

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	IV • 100 mg	More Frequent: • Infusion-related reactions (fever/chills, and headache) Less Frequent • Anemia • Leukopenia • Respiratory distress • Thrombocytopenia • Renal function impairment	• GI disturbance (loss of appetite, nausea, vomiting, diarrhea, abdominal pain)	Monitor BUN, Cr, CBC, electrolytes, and LFTs. Infuse diluted solution at a rate of 2.5 mg/kg/hour. To minimize immediate infusion-related reactions, premedicate with the following 30 to 60 minutes prior to administration: acetaminophen, diphenhydramine, and/or hydrocortisone. Adequate hydration and pre-infusion administration of NS may decrease risk of nephrotoxicity. In-line filters should not be used. Do not dilute with saline solutions or mix with other drugs or electrolytes (compatibility has not been established). Use with caution with bone marrow suppressants or other nephrotoxic drugs; renal toxicity is dose-dependent, but less renal toxicity than seen with conventional amphotericin B. Consider dose reduction in children with impaired renal function.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Amphotericin B Liposome	IV • 50 mg	More Frequent • Fever, chills • Hypokalemia Less Frequent • Back pain • Chest pain • Dark urine • Dyspnea • Infusion-related reaction (headache) • Jaundice • Renal function impairment Rare • Anaphylactic reaction	• GI disturbance (nausea, vomiting, diarrhea, abdominal pain) • Headache • Rash	Monitor BUN, Cr, CBC, electrolytes, and LFTs. Infuse over 2 hours. Do not use in-line filter less than 1 micron to administer. Consider dose reduction in children with impaired renal function. Flush line with D5W before and after infusion.
Artesunate	IV • Please refer to the AMIVAS website.	Rare • Anaphylactic reaction • Neutropenia • Bradycardia	• GI disturbance (nausea, vomiting) • Headache • Rash	Monitor CBC, LFTs, and electrolytes. Artesunate is preferred over quinidine for severe malaria because of decreased mortality. Monitor signs and symptoms of hemolytic anemia, Hb, and renal function for 4 weeks after therapy.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Atovaquone	Oral Suspension • 150 mg/mL	Frequent • Fever • Rash	Frequent • GI disturbances (nausea, vomiting, diarrhea) • Headache • Cough • Insomnia	Should be administered with a meal to enhance absorption; bioavailability increases threefold when administered with a high-fat meal. Avoid suspension in neonates due to benzyl alcohol. Monitor CBC with differential, liver enzymes, bilirubin, serum electrolytes, and serum amylase.
Atovaquone/ Proguanil	Tablets • Pediatric tablets; 62.5 mg/25 mg • Adult tablets; 250 mg/100 mg	Less Frequent • Vomiting • Pruritus	N/A	Pediatric tablets are available to make dosing easier. Atovaquone taken with a high-fat meal significantly increases the rate and extent of absorption. Side effects requiring discontinuation in ~1% to 2% of people.[b] Not recommended for prophylaxis in children with CrCl <30 mL/min.
Azithromycin	Oral Suspension • 20 mg/mL • 40 mg/mL Tablets • 250 mg	More Frequent • Thrombophlebitis (IV form) Rare • Acute interstitial nephritis	• GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) • Dizziness, headache	Administer 1 hour before or 2 hours after a meal; do not administer with aluminum- and magnesium-containing antacids.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	• 500 mg • 600 mg Oral Powder Packet • 1,000 mg IV • 500 mg	• Allergic reactions/anaphylaxis (dyspnea, hives, rash) • Pseudomembranous colitis • Prolonged QT interval • Syncope • Torsades de pointes • Ventricular tachycardia		IV should be infused at a concentration of 1 mg/mL over a 3-hour period, or 2 mg/mL over a 1-hour period; IV should not be administered as a bolus. Use with caution in children with hepatic function impairment; biliary excretion is the main route of elimination. Potential drug interactions. See Table 5. Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for more information.
Bedaquiline	Tablets • 20 mg • 100 mg	Less Frequent • Chest pain • Hemoptysis Rare • Prolonged QT interval on ECG • Hepatotoxicity	More Frequent • Arthralgia • Nausea Less Frequent • Anorexia • Rash Rare • Increased serum amylase	Monitor serum potassium, calcium, and magnesium at baseline. Monitor ALT, AST, alkaline phosphatase, and bilirubin at baseline and monthly during treatment. Monitor EKG at baseline and monthly during treatment. Give with food (standard meal approximately 22 g of fat and 558 calories) to increase bioavailability twofold.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Capreomycin	IV/IM • 1,000 mg	More Frequent • Nephrotoxicity Less Frequent • Hypersensitivity (rash, fever) • Hypokalemia • Neuromuscular blockade • Ototoxicity, both auditory and vestibular • Injection site pain, sterile abscess	N/A	Rarely used in the United States because of efficacy concerns. Administer only by deep IM injection into large muscle mass (superficial injections may result in sterile abscess). Requires dose adjustment in children with impaired renal function. Monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy. Monitor LFTs and electrolytes.
Caspofungin	IV • 50 mg • 70 mg	More Frequent • Histamine-mediated symptoms (fever, facial swelling, pruritus, bronchospasm) Rare • Hypokalemia • Anaphylactic reaction	• GI disturbances (nausea, vomiting, diarrhea) • Headache • Rash, facial flushing • Elevated ALTs and ASTs • Thrombophlebitis	Requires dose adjustment in moderate-to-severe hepatic insufficiency. Administer IV infusion over 1 hour in normal saline (do not use diluents containing dextrose). Higher doses (150 mg or greater) should be infused over at least 2 hours.
Chloroquine Phosphate	Tablets • 500 mg • 250 mg	More Frequent • Pruritus: Common in individuals of Black race	• Psoriasis exacerbations • GI disturbances (nausea, vomiting, diarrhea)	Store in child-proof containers and protect from light. Overdose can be toxic.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		Less Frequent, but More Severe • Auditory toxicity • Ocular toxicity • Neuropsychiatric disorders • QT prolongation • Hepatitis • Bone marrow suppression • Peripheral neuropathy	• Visual disturbances including photosensitivity • Muscle weakness	Chloroquine phosphate is bitter tasting, so consider administering with foods such as chocolate syrup that can mask the taste. Use with caution in children with G6PD deficiency or seizure disorder. Genetic testing is recommended. Monitor CBC; periodic neurologic and ophthalmologic exams are recommended in children on prolonged therapy. Monitor EKG at baseline and as clinically indicated in children with elevated risk of QT prolongation.
Cidofovir	IV • 370 mg	More Frequent • Nephrotoxicity • Neutropenia Less Frequent • Fever and allergic reactions Rare • Vision changes due to ocular hypotony • Metabolic acidosis	• GI disturbances (anorexia, diarrhea, nausea, vomiting) • Headache • Asthenia • Proteinuria	Infuse over 1 hour. Should not be used in children with severe renal impairment. Nephrotoxicity risk is decreased with prehydration with IV NS 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.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				Concurrent use of other nephrotoxic drugs should be avoided. Perform ophthalmologic exams and monitor renal function, urinalysis, electrolytes, and CBC.
Ciprofloxacin	Oral Suspension • 50 mg/mL • 100 mg/mL Tablets • 100 mg • 250 mg • 500 mg • 750 mg XR Tablets • 500 mg • 1,000 mg IV • 200 mg • 400 mg	Less Frequent • Phototoxicity Rare • CNS stimulation • Hepatotoxicity • Hypersensitivity reactions (rash, pruritus, and exfoliative skin disorders including SJS, dyspnea, and vasculitis) • Interstitial nephritis • Phlebitis (at injection sites) • Pseudomembranous colitis • Tendonitis or tendon rupture • QT interval prolongation	More Frequent • GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) • CNS toxicity (dizziness, headache, insomnia, drowsiness) Less Frequent • Change in taste • Photosensitivity	Administer oral formulations at least 2 hours before or 6 hours after taking sucralfate, 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. Possible phototoxicity reactions with sun exposure. IV infusions should be over 1 hour. Do not split, crush, or chew XR tablets. QT prolongation is concentration-dependent and occurs with use of two or more medications that prolong QT interval.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Clarithromycin	Oral Suspension • 25 mg/mL • 50 mg/mL Tablets • 250 mg • 500 mg	Rare • Hepatotoxicity • Hypersensitivity reaction (rash, pruritus, dyspnea) • Pseudomembranous colitis • Thrombocytopenia • QT interval prolongation	More Frequent • GI disturbances (abdominal discomfort or pain, diarrhea, nausea, vomiting) Less Frequent • Abnormal taste sensation • Headache • Rash	Requires dose adjustment in children with impaired renal function. Can be administered without regard to meals. Reconstituted suspension should not be refrigerated. Potential drug interactions exist. See Table 5. Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections and Drug-Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for more information.
Clindamycin	Oral Solution • 15 mg/mL Capsules • 75 mg • 150 mg • 300 mg	More Frequent • Pseudomembranous colitis Less Frequent • Hypersensitivity (rash, redness, pruritus) • Neutropenia • Thrombocytopenia	More Frequent • GI disturbances (abdominal pain, nausea, vomiting, diarrhea) Less Frequent • Fungal overgrowth in rectal and genital areas	IV preparation not recommended for use in neonates because of benzyl alcohol. IV preparation must be diluted prior to administration. Do not exceed 600 mg in a single IM injection.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	IV/IM • 300 mg • 600 mg • 900 mg			Capsule formulation should be taken with food or a full glass of water to avoid esophageal irritation. Reconstituted oral solution should not be refrigerated. Some products may contain tartrazine and can cause allergic reactions. Allergic reactions are frequently observed in people who also have aspirin hypersensitivity.
Cycloserine	Capsule • 250 mg	More Frequent • CNS toxicity (including confusion, anxiety) Less Frequent • Hypersensitivity (skin rash) • Peripheral neuropathy • Seizures • Psychosis Rare • Cardiac arrhythmias	More Frequent • Headache, dizziness, drowsiness Rare • Photosensitivity	Take with food to minimize gastric irritation. Neurotoxicity is related to excessive serum concentrations; serum concentrations should be maintained at 25–30 mcg/mL. Monitor serum levels if possible. Requires dose adjustment in children with impaired renal function. Do not administer to children with severe renal impairment (because of increased risk of neurotoxicity). Should coadminister pyridoxine at the same time.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				May increase Vitamin B12 and folic acid requirements. Monitor renal function, LFTs, and CBC.
Dapsone	Oral Suspension (extemporaneously prepared from 25 mg tablets) • 2 mg/mL Tablets • 25 mg • 100 mg	More Frequent • Hemolytic anemia (especially with G6PD deficiency) • Methemoglobinemia • Skin rash Rare • Blood dyscrasias • Exfoliative skin disorders (including SJS) • Hepatic toxicity • Mood or other mental changes • Peripheral neuritis • Hypersensitivity reaction (fever, rash, jaundice, anemia)	• CNS toxicity (headache, insomnia, nervousness) • GI disturbances (anorexia, nausea, vomiting) • Photosensitivity reactions	Protect from light; dispense syrup in amber glass bottles. Monitor CBC and LFTs. Use with caution in children with G6PD deficiency, Hb M deficiency, and methemoglobin reductase deficiency.
Doxycycline	Tablets and Capsules • 20 mg • 50 mg • 75 mg • 100 mg	More Frequent • GI irritation, pill esophagitis • Photosensitivity Less Frequent • Increased intracranial pressure	• Staining of teeth possible for individuals aged <8 years • Photo-onycholysis • GI disturbances (nausea, vomiting, abdominal cramps)	Swallow with adequate amounts of fluids. Avoid antacids, milk, dairy products, and iron for 1 hour before and 2 hours after administration of doxycycline.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	Oral Suspension and Syrup • 5 mg/mL oral suspension • 10 mg/mL oral syrup IV • 100 mg	• Photosensitivity • Hemolytic anemia • Rash and hypersensitivity reactions • *Clostridium difficile*-associated diarrhea • Pseudotumor cerebri		Avoid high-fat meals that can reduce doxycycline serum levels. Use with caution in hepatic and renal disease. IV doses should be infused over 1 to 4 hours. Children should avoid prolonged exposure to direct sunlight (skin sensitivity). Monitor renal function, CBC, and LFTs if therapy is prolonged.
Erythromycin	Erythromycin-Base Tablet • 250 mg • 333 mg • 500 mg DR Tablet • 250 mg • 333 mg • 500 mg DR Capsule • 250 mg	Less Frequent • Estolate may cause cholestatic jaundice, although hepatotoxicity is uncommon (2% of reported cases). Rare • QT prolongation • Hypersensitivity reactions (rash, exfoliative skin disorders including SJS/TEN)	• GI disturbances (nausea, vomiting, abdominal cramps) • Rash, urticaria • Increased LFTs	Use with caution in liver disease. Oral therapy should replace IV therapy as soon as possible. Give oral doses after meals. Parenteral administration should consist of a continuous drip or slow infusion over 1 hour or longer. Adjust dose in renal failure. Erythromycin should be used with caution in neonates; hypertrophic pyloric stenosis and life-threatening episodes of ventricular tachycardia associated with prolonged QTc interval have been reported.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	Erythromycin Ethyl Succinate *Suspension* • 200 mg/5 mL • 400 mg/5 mL *Oral Drops* • 100 mg/2.5 mL *Chewable Tablet* • 200 mg *Tablet* • 400 mg Erythromycin Estolate *Suspension* • 125 mg/5 mL • 200 mg/5 mL Erythromycin Stearate *Tablet* • 250 mg • 500 mg			IV formulations contain benzyl alcohol derivatives and are not recommended in neonates.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	Erythromycin Gluceptate *IV* • 200 mg Erythromycin Lactobionate *IV* • 500 mg • 1,000 mg			
Ethambutol	Tablets • 100 mg • 400 mg	Less Frequent • Acute gouty arthritis (secondary to hyperuricemia) Rare • Hypersensitivity (rash, fever, joint pain) • Peripheral neuropathy • Retrobulbar optic neuritis, decreased visual acuity, loss of red-green color discrimination • Bone marrow suppression • Abnormal LFTs, hepatotoxicity	• GI disturbances (abdominal pain, anorexia, nausea, vomiting) • Confusion • Disorientation • Headache	Requires dose adjustment in children with impaired renal function. Take with food (e.g., gelatin, chocolate pudding) to minimize gastric irritation. Tablets may be crushed. Monitor visual acuity and red-green color discrimination. Document normal vision at baseline. Monitor renal function, LFTs, and CBC. Avoid concomitant use of neurotoxic drugs. Evaluate pregnancy status prior to treatment.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Ethionamide	Tablet • 250 mg	Less Frequent • Hepatitis, jaundice • Peripheral neuritis • Psychiatric disturbances Rare • Goiter or hypothyroidism • Hypoglycemia • Optic neuritis • Rash	More Frequent • GI disturbances (anorexia, metallic taste, nausea, vomiting, stomatitis) • Orthostatic hypotension Rare • Gynecomastia	Avoid use of other neurotoxic drugs that could increase potential for peripheral neuropathy and optic neuritis. Administration of pyridoxine may alleviate peripheral neuritis. Avoid alcohol. Take with food to minimize gastric irritation. Monitor LFTs, glucose, and thyroid function. Perform periodic ophthalmologic exams. Monitor for signs and symptoms of SCARs.
Fluconazole	Oral Suspension • 10 mg/mL • 40 mg/mL Tablets • 50 mg • 100 mg • 150 mg • 200 mg IV • 200 mg	Less Frequent • Hypersensitivity (fever, chills, rash) Rare • Agranulocytosis, eosinophilia, leucopenia, thrombocytopenia • Exfoliative skin disorders (including SJS) • Hepatotoxicity • QT prolongation • Thrombocytopenia	More Frequent • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) Less Frequent • CNS effects (dizziness, drowsiness, headache) • Alopecia	Can be given orally without regard to meals. Shake suspension well before dosing. Requires dose adjustment in children with impaired renal function. IV administration should be administered over 1–2 hours at a rate of ≤200 mg/hour. Daily dose is the same for oral and IV administration.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	• 400 mg			Multiple potential drug interactions exist. See Table 5. Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections and Drug-Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for more information. Monitor periodic LFTs, renal function, and CBC.
Flucytosine	Capsules • 250 mg • 500 mg Oral Liquid • Extemporaneous preparation	More Frequent • Bone marrow suppression (especially leukopenia and thrombocytopenia) Less Frequent • Hepatotoxicity • Renal toxicity (including crystalluria) Rare • Cardiac toxicity (ventricular dysfunction, myocardial toxicity, cardiac arrest) • CNS symptoms (hallucinations, seizures, peripheral neuropathy) • Anaphylaxis • Hearing loss	• GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) • Elevated ALTs and ASTs • Rash Rare • CNS symptoms (headache, drowsiness, confusion, vertigo)	Monitor serum concentrations and adjust dose to maintain therapeutic levels and minimize risk of bone marrow suppression. Requires dose adjustment in children with impaired renal function; use with extreme caution. Fatal aplastic anemia and agranulocytosis rarely have been reported. Consider determination of dihydropyridine dehydrogenase (DPD) enzyme deficiency in children who develop drug toxicity.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				Oral preparations should be administered with food over a 15-minute period to minimize GI side effects. QT prolongation may occur. Monitor CBC, LFTs, renal function, and electrolytes.
Foscarnet	IV • 6,000 mg	More Frequent • Nephrotoxicity • Serum electrolyte abnormalities (hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia) Less Frequent • Hematologic toxicity (anemia, granulocytopenia) • Neurotoxicity (muscle twitching, tremor, seizures, tingling around mouth) • Cardiac abnormalities secondary to electrolyte changes • Phlebitis (at site of injection) Rare • Sores or ulcers in mouth or throat	Frequent • GI disturbances (abdominal pain, anorexia, nausea, vomiting) • Anxiety, confusion, dizziness, headache • Fever	Requires dose adjustment in children with impaired renal function. Use adequate hydration to decrease nephrotoxicity. Avoid concomitant use of other drugs with nephrotoxicity. Monitor serum electrolytes, ECG, renal function, and CBC. IV solution of 24 mg/mL can be administered via central line; must be diluted to a final concentration ≤12 mg/mL if given via peripheral line. Must be administered at a constant rate by infusion pump over ≥2 hours (or no faster than 1 mg/kg/minute).

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Ganciclovir	Capsules • 250 mg • 500 mg IV • 500 mg	More Frequent • Granulocytopenia • Thrombocytopenia Less Frequent • Anemia • CNS effects (confusion, headache) • Hypersensitivity (fever, rash) • Elevated transaminase enzymes • Increase in creatinine, BUN • Phlebitis (at injection sites) Rare • Retinal detachment • Seizures • Psychosis • Cardiovascular effects (hypertension, chest pain)	• GI disturbances (abdominal pain, anorexia, nausea, vomiting) • Rash	Requires dose adjustment in children with renal impairment. Avoid other nephrotoxic drugs. IV infusion over at least 1 hour; in-line filter required. Flush line well with NS before and after administration. Maintain good hydration. Undiluted IV solution is alkaline (pH 11); use caution when handling and preparing solutions, and avoid contact with skin and mucus membranes. Administer oral doses with a high-fat meal to increase absorption. Do not open or crush capsules. Perform ophthalmologic examinations and monitor CBC, LFTs, and renal function.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Imipenem/Cilastatin	IV • 250 mg • 500 mg	More Frequent • Hematologic toxicity (decreased hematocrit, decreased hemoglobin) • Hepatotoxicity (increased ALT and AST) Less Frequent • Hematologic toxicity (eosinophilia, thrombocythemia) • Renal toxicity (proteinuria) Rare • Seizures • Cardiovascular toxicity • Neutropenia • Phlebitis near injection site	Rare • Rash • GI disturbances (nausea and vomiting) • Oral candidiasis	Administer by IV intermittent infusion. Doses ≤500 mg may be infused over 20 to 30 minutes. Doses >500 mg should be infused over 40 to 60 minutes. If nausea and vomiting occur during infusion, decrease rate of IV infusion.
Isavuconazole	Oral Capsules • 74.5 mg • 186 mg IV • 372 mg	More Frequent • Peripheral edema • Hypokalemia Less Frequent • Increase in liver enzymes	More Frequent • Back pain • GI disturbances (abdominal pain and constipation) Less Frequent • Anxiety	Administer IV over a minimum of 1 hour via infusion, set with in-line filter. Give capsules with or without food. Swallow capsules whole. Do not chew, crush, dissolve, or open capsules.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		Rare • Atrial fibrillation • Cholelithiasis • Acute respiratory failure	Rare • Dermatologic (alopecia, urticaria) • Tinnitus	Some dosage forms contain propylene glycol. Large amounts administered have been associated with potentially fatal toxicities in neonates, including metabolic acidosis, seizures, renal failure, and CNS depression.
Isoniazid	Oral Syrup • 10 mg/mL Tablets • 100 mg • 300 mg IV/IM • 100 mg	More Frequent • Hepatitis prodromal syndrome (anorexia, weakness, vomiting) • Hepatitis • Peripheral neuritis Rare • Blood dyscrasias • Hypersensitivity (fever, rash, joint pain) • Neurotoxicity (including seizure) • Optic neuritis	• GI disturbances (abdominal pain, nausea, vomiting, diarrhea) • Elevated liver transaminases • Pyridoxine deficiency	Take with food to minimize gastric irritation. Take ≥1 hour before aluminum-containing antacids. Avoid taking isoniazid with histamine and tyramine-containing foods. Increase dietary intake of folate, niacin, and magnesium. Use with caution in children with hepatic function impairment, severe renal failure, or history of seizures. Pyridoxine supplementation should be provided for all children with HIV. Monitor LFTs and perform periodic ophthalmologic examinations.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Itraconazole	Oral Solution • 10 mg/mL Capsule • 100 mg IV • 250 mg	Less Frequent • Hypersensitivity (fever, chills, rash) • Hypokalemia (can be associated with cardiac arrhythmias) Rare • Hepatotoxicity • Hematologic abnormalities (thrombocytopenia, leukopenia)	More Frequent • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) Less Frequent • CNS effects (dizziness, drowsiness, headache) • Rash	Oral Solution • Give on an empty stomach because gastric acid increases absorption. Capsule • Administer after a full meal to increase absorption. • Grapefruit juice may alter itraconazole levels. Itraconazole oral solution has 60% greater bioavailability compared with capsules, and the oral solution and capsules should not be used interchangeably. Administer IV infusion over at least 1 hour. Multiple potential drug interactions. See Table 5. Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections and Drug-Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for more information. Monitor LFTs and potassium levels.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				Monitor serum concentrations (TDM) in severe infections after 2 weeks of therapy. Levels may be drawn any time during the dosing interval. Box warning: May cause or exacerbate HF. Discontinue to reassess risk-benefit if signs or symptoms of HF occur.
Kanamycin	IV/IM • 75 mg • 500 mg • 1,000 mg	More Frequent • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Ototoxicity (both auditory and vestibular) Less Frequent • Hypersensitivity (rash, redness, or swelling) Rare • Neuromuscular blockade	N/A	Must be infused over 30 to 60 minutes to avoid neuromuscular blockade. Requires dose adjustment in children with impaired renal function. Monitor renal function and auditory function periodically (e.g., monthly) in children on prolonged therapy. Monitor serum concentrations (TDM).

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Ketoconazole	Tablet • 200 mg Topical • Shampoo • Cream • Gel • Foam Oral Suspension • Extemporaneous preparation	Less Frequent • Hypersensitivity (fever, chills, rash) Rare • Hepatotoxicity (including hepatic failure)	More Frequent • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) Less Frequent • CNS effects (dizziness, drowsiness, headache) Rare • Gynecomastia • Impotence • Menstrual irregularities • Photophobia	Adverse GI effects occur less often when administered with food. Drugs that decrease gastric acidity or sucralfate should be administered ≥2 hours after ketoconazole. Administer with acidic liquid (non-diet cola or orange juice) in children with achlorhydria. Disulfiram-like reactions have occurred in pediatric patients accidentally ingesting alcohol. Hepatotoxicity is an idiosyncratic reaction, usually reversible when stopping the drug, but rare fatalities can occur any time during therapy; more common in females and adults >40 years, but cases have been reported in children. High-dose ketoconazole suppresses corticosteroid secretion and lowers serum testosterone concentration (reversible). Multiple potential drug interactions exist. Monitor LFTs.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Mefloquine	Tablet • 250 mg	More Frequent • CNS effects (psychosis, depression, hallucinations, paranoia, seizures) Rare • Blood dyscrasias • Cholestasis, elevated bilirubin	• Rash • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) • Minor CNS effects (dizziness, vivid dreams, insomnia) • Tinnitus, blurred vision	Side effects are less prominent in children. Administer with food and plenty of water. Tablets can be crushed and added to food; administer with foods such as chocolate syrup or gelatin to mask the bitter taste of crushed tablets. Monitor LFTs.
Nitazoxanide	Oral Suspension • 20 mg/mL Tablet • 500 mg	N/A	More Frequent • GI disturbances (abdominal pain, nausea, vomiting) • Headache Rare • Scleral icterus • Rash	Should be given with food. Shake suspension well prior to dosing. Use with caution in neonates. Nitazoxanide products may contain benzyl alcohol derivatives that can be associated with gasping syndrome.
p-Aminosalicylic Acid	DR Granules • 4,000 mg per packet	Rare • Hypersensitivity o Fever o Rash o Exfoliative dermatitis o GI symptoms	• GI disturbances (abdominal pain, nausea, vomiting, diarrhea)	Should not be administered to children with severe renal disease. Drug should be discontinued at first sign of hypersensitivity reaction (rash, fever, and GI symptoms typically precede jaundice).

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		o Jaundice o Hepatitis o Pericarditis o Vasculitis o Hematologic abnormalities including hemolytic anemia o Hypoglycemia o Optic neuritis o Encephalopathy o Reduction in Prothrombin • Crystalluria • Hemolytic anemia		Vitamin B12 therapy should be considered in children receiving for >1 month. Administer granules by sprinkling on acidic foods (e.g., applesauce, yogurt) or a fruit drink (e.g., tomato juice, orange juice). Maintain urine at neutral or alkaline pH to avoid crystalluria. The granule's soft "skeleton" may be seen in the stool. Monitor CBC and LFTs.
Pentamidine	IV/IM/Aerosol • 300 mg	For IV Administration *More Frequent* • Nephrotoxicity • Hypoglycemia • Hyperglycemia or diabetes mellitus • Elevated liver transaminases • Hypotension • Leukopenia or neutropenia • Thrombocytopenia	For IV Administration *More Frequent* • GI disturbances (anorexia, nausea, vomiting, diarrhea) *Less Frequent* • Unpleasant metallic taste For Aerosol Administration *More Frequent* • Bronchospasm	Rapid infusion may result in precipitous hypotension; IV infusion should be administered over ≥1 hour (preferably 2 hours). 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 retreatment within 3 months of prior treatment.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		Less Frequent • Anemia • Cardiac arrhythmias • Hypersensitivity (skin rash, fever) • Pancreatitis • Phlebitis • Sterile abscess (at site injection) For Aerosol Administration *More Frequent* • Sneezing • Cough		Hyperglycemia and diabetes mellitus can occur up to several months after drug is discontinued. Monitor LFTs, renal function, glucose, electrolytes, and BP. Inhalation • A special nebulizer is required for aerosol administration. Medical personnel should be trained in the proper administration of aerosolized pentamidine. • An inhaled bronchodilator may be administered prior to each dose in children who experience bronchospasm or cough.
Posaconazole	IR Oral Suspension • 40 mg/mL Oral Powder Packet • 300 mg DR Tablet • 100 mg DR Oral Suspension • Extemporaneous preparation	Less Frequent • Hypersensitivity (fever, chills, skin rash) • Anaphylactoid reaction with IV infusion Rare • Hepatotoxicity (including hepatic failure) • Exfoliative skin disorders (including SJS)	• Bone marrow suppression • Muscular pain • CNS effects (headache, dizziness, fatigue) • Elevated serum ALTs and ASTs	Must be given with meals to ensure adequate absorption. Monitor LFTs, renal function, and electrolytes. Monitor serum drug concentrations (TDM). Shake suspension prior to dosing. Various oral formulations are not interchangeable.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
	IV • 300 mg	• Renal dysfunction • Cardiac arrhythmias (QT interval prolongation, Torsades de pointes, hypertension) • Hemolytic uremic syndrome • Pulmonary embolism • Neutropenia		Administer reconstituted DR suspension within 1 hour of prep and administer with food. Administer IR suspension during or within 20 minutes following a full meal. Infuse IV over 90 minutes via central line only.
Primaquine	Tablet • 15 mg (base) = 26.3 mg primaquine phosphate	More Frequent • Hemolytic anemia (with G6PD deficiency) Less Frequent • Methemoglobinemia Rare • Leukopenia	• GI disturbances (nausea, vomiting)	Take with meals or antacids to minimize gastric irritation. Store in a light-resistant container. Combat bitter taste with chocolate syrup, applesauce, or jelly. Monitor CBC. Recommend G6PD testing.
Pyrazinamide	Tablet • 500 mg Oral Suspension • Extemporaneous preparation	More Frequent • Arthralgia Less Frequent • Hepatotoxicity (dose-related) Rare • Acute gouty arthritis secondary to hyperuricemia • Thrombocytopenia, anemia	• Skin rash, pruritus • Photosensitivity • Malaise • GI disturbances (nausea, vomiting) • Arthralgia • Hyperuricemia	Avoid in children with severe hepatic impairment. Reduce dose in children with renal or hepatic impairment. Monitor LFTs and uric acid.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
		• Interstitial nephritis • Porphyria		
Pyrimethamine	Tablet • 25 mg Oral Suspension • Extemporaneous preparation	Less Frequent • Neutropenia • Thrombocytopenia • Megaloblastic anemia Rare • SJS • Seizure	• Skin rash • Photosensitivity • Dry mouth • GI disturbances (nausea, vomiting) • CNS effects (depression, insomnia)	To prevent hematologic toxicity, administer with leucovorin. Monitor CBC. Administer with meals to avoid GI side effects. Recommend G6PD testing.
Quinidine	Tablet (XR) • 324 mg Tablet • 200 mg • 300 mg	Serious • Cardiac arrhythmias • QT interval prolongation • Hypoglycemia • Hemolytic anemia (with G6PD deficiency) • Hepatotoxicity	Very Frequent • Cinchonism (dose-dependent)—syndrome of tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium.	Monitor CBC and LFTs. Hemolysis may occur in children with G6PD.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Ribavirin	Powder for Solution for Nebulization • Reconstituted product contains 20 mg/mL. Oral Solution • 40 mg/mL Capsule • 200 mg Tablets • 200 mg • 400 mg • 600 mg	More Frequent • Hemolytic anemia (with associated potential for increase in unconjugated bilirubin and uric acid) Less Frequent • Neutropenia, thrombocytopenia, anemia • Pancreatitis	• CNS effects (fatigue, headache, insomnia, depression) • GI disturbances (abdominal pain, nausea, vomiting) • Skin rash • Myalgia, arthralgia, weakness	Should not be used in children with severe renal impairment. Should not be used as monotherapy for treatment of hepatitis C but rather, used in combination with IFN-α. Intracellular phosphorylation of pyrimidine nucleoside analogues (zidovudine, stavudine, zalcitabine) decreased by ribavirin, may have antagonism; use with caution. Enhances phosphorylation of didanosine; use with caution due to increased risk of pancreatitis/ mitochondrial toxicity. Oral solution contains propylene glycol. This drug is teratogenic/embryocidal and contraindicated in pregnant women and their partners. Avoid pregnancy for an additional 6 months after treatment. In combination therapy with IFN-α, ribavirin may cause a reduction in growth velocity in children and adolescents 5–17 years of age.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				Monitor CBC, renal function, LFTs, and thyroid function. Perform pregnancy tests regularly while on therapy. High-fat meals increase AUC and Cmax. Be consistent with fat content of meals.
Rifabutin	Capsule • 150 mg Oral Suspension • Extemporaneous preparation	More Frequent • Allergic reaction (rash, pruritus) • Neutropenia Less Frequent • Asthenia Rare • Arthralgia, myalgia • Change in taste • Pseudojaundice • Thrombocytopenia • Uveitis	• Headache • Insomnia • Rash, staining of skin • GI disturbances (abdominal pain, diarrhea, nausea, vomiting, anorexia)	Preferably take on an empty stomach, but may be administered with food in children with GI intolerance. The contents of capsules may be mixed with applesauce for children who are unable to swallow capsules. May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses). Uveitis seen with high-dose rifabutin (i.e., >300 mg/day in adults), especially when combined with clarithromycin. Multiple potential drug interactions exist. Use with caution in children with renal or hepatic impairment.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				Monitor CBC and LFTs; conduct ophthalmologic examinations. Reduce dose in children with renal impairment.
Rifampin	Oral Suspension • Extemporaneous preparation Capsules • 150 mg • 300 mg IV • 600 mg	Less Frequent • Flu-like syndrome Rare • Blood dyscrasias • Hepatitis prodromal syndrome (anorexia, nausea, vomiting, weakness) • Hepatitis • Interstitial nephritis • Exfoliative skin disorders (including SJS)	• GI disturbances (abdominal pain, diarrhea) • CNS effects (fatigue, headache, insomnia, depression) • Rash • Discoloration of body fluids • Elevated serum transaminases • Visual changes	Preferably taken on an empty stomach, but can be administered with food in children with GI intolerance; take with full glass of water. Suspension formulation stable for 30 days. Shake well prior to dosing. May mix contents of capsule with applesauce or jelly. May cause reddish to brown-orange color urine, feces, saliva, sweat, skin, or tears (can discolor soft contact lenses). Multiple potential drug interactions Use with caution in children with hepatic impairment. Administer IV by slow infusion. Extravasation may cause local irritation and inflammation. Monitor CBC and LFTs.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Streptomycin	IV/IM • 1,000 mg	More Frequent • Nephrotoxicity • Neurotoxicity (including muscle twitching, seizures) • Peripheral neuritis • Ototoxicity (both auditory and vestibular) Less Frequent • Hypersensitivity (skin rash, redness, or swelling) • Optic neuritis • Bone marrow suppression Rare • Neuromuscular blockade	• CNS effects (headache, ataxia, dizziness)	Usual route of administration is deep IM injection into large muscle mass. For children who cannot tolerate IM injections, dilute to 12–15 mg in 100 mL of 0.9% sodium chloride; must be infused over 30–60 minutes to avoid neuromuscular blockade. Requires dose adjustment in children with impaired renal function. Monitor renal function and hearing periodically (e.g., monthly) in children on prolonged therapy. Monitor serum concentrations (TDM).
Sulfadiazine	Tablet • 500 mg Oral Suspension • Extemporaneous preparation	Rare • Crystalluria, renal failure • Bone marrow suppression/blood dyscrasias • Severe hypersensitivity syndrome • Hemolytic anemia (with G6PD deficiency)	• GI disturbances (abdominal pain, diarrhea, nausea) • CNS effects (headache, dizziness) • Rash • Photosensitivity	Ensure adequate fluid intake to avoid crystalluria. Monitor CBC, renal function, and urinalysis. Monitor serum concentrations (TDM) if serious infection.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
				May potentially lead to hyperbilirubinemia and kernicterus in neonates and young infants. Avoid use in infants <2 months unless other options are not available.
Trimethoprim-Sulfamethoxazole (TMP-SMX)	Oral Suspension • TMP 8 mg/mL and SMX 40 mg/mL Tablets *Single Strength* • TMP 80 mg and SMX 400 mg *Double Strength* • TMP 160 mg and SMX 800 mg IV • TMP 16 mg/ mL and SMX 80 mg/mL	More Frequent • Skin rash Less Frequent • Hypersensitivity reactions (skin rash, fever) • Hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anemia) Rare • Exfoliative skin disorders (including SJS) • Hemolytic anemia (with G6PD deficiency) • Methemoglobinemia • Renal toxicity (crystalluria, nephritis, tubular necrosis) • CNS toxicity (aseptic meningitis) • Pseudomembranous colitis • Cholestatic hepatitis • Thyroid function disturbance	• GI disturbances (anorexia, nausea, vomiting, diarrhea) • Photosensitivity • Rash	Requires dose adjustment in children with impaired renal function. Maintain adequate fluid intake to prevent crystalluria and stone formation; take with full glass of water. Potential for photosensitivity skin reaction with sun exposure. May displace bilirubin from protein binding sites which may lead to hyperbilirubinemia in neonates and young infants. Oral suspension may contain propylene glycol that can lead to fatal toxicities, such as metabolic acidosis, renal failure, or respiratory depression in neonates. Administer IV infusion over 60–90 minutes. Monitor CBC and renal function.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Valacyclovir	Tablets • 500 mg • 1,000 mg Note: An oral suspension formulation of 50 mg/mL can be prepared in Ora-Sweet or SyrPalta syrups)	Rare • Renal failure • Bone marrow suppression • Thrombotic microangiopathy/ hemolytic uremic syndrome • CNS effects (psychosis, seizures, delirium)	More Frequent • Headache, nausea Less Frequent • Arthralgia • Dizziness, fatigue • GI disturbances (diarrhea or constipation, anorexia, abdominal pain, vomiting) • Dysmenorrhea	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in adults with HIV with advanced disease receiving high (i.e., 8 g/day) but not low doses. Monitor CBC and renal function. Avoid other nephrotoxic drugs. Maintain adequate hydration.
Valganciclovir	Tablet • 450 mg Oral Solution • 50 mg/mL	More Frequent • Granulocytopenia • Thrombocytopenia Less Frequent • Anemia • CNS effects (seizures, psychosis, hallucinations) • Hypersensitivity (fever, rash) • Elevated transaminase enzymes • Increase in creatinine or BUN • Retinal detachment	• GI disturbances (abdominal pain, anorexia, nausea, vomiting) • CNS effects (headache, insomnia)	Requires dose adjustment in children with renal impairment. Avoid other nephrotoxic drugs. Tablets should not be broken or crushed. Monitor CBC and renal function. Potentially teratogenic and carcinogenic.

Drug	Preparations	Major Toxicities[a]		Special Instructions
		Indicating Need for Medical Attention	Indicating Need for Medical Attention If Persistent or Bothersome	
Voriconazole	Tablets • 50 mg • 200 mg Oral Suspension • 40 mg/mL IV • 200 mg	Less Frequent • Hypersensitivity (fever, chills, skin rash) • Anaphylactoid reaction with IV infusion Rare • Hepatotoxicity (including hepatic failure) • Exfoliative skin disorders (including SJS) • Renal dysfunction • Cardiac arrhythmias • Pancreatitis • QT prolongation • Electrolyte abnormalities • Optic neuritis, papilledema	More Frequent • Visual changes, dose-related (photophobia, blurry vision) • CNS effects (dizziness, drowsiness, headache) • GI disturbances (abdominal pain, constipation, diarrhea, anorexia, nausea, vomiting) • Photosensitivity Rare • Gynecomastia • Elevated serum transaminases	Oral tablets should be taken 1 hour before or after a meal. Shake oral suspension well prior to dosing. Maximum IV infusion rate should be 3 mg/kg/hour over 1–2 hours. Use oral administration for children with impaired renal function, if possible, because of accumulation of IV vehicle in children with renal insufficiency. Dose adjustment is needed if hepatic insufficiency exists. Visual disturbances are common (>30%) but are transient and reversible when drug is discontinued. Multiple potential drug interactions exist. Monitor renal function, electrolytes, and LFTs. 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.

[b] Source: Atovacquone/Proguanil. ScienceDirect. https://www.sciencedirect.com/topics/medicine-and-dentistry/atovaquone-proguanil.

Key: ALT = alanine transaminase; AST= aspartate transaminase; AUC = area under the curve; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; C_{max} = maximum plasma concentration; CNS = central nervous system; Cr = creatinine; CrCl = creatinine clearance; D5W = dextrose 5% in water; DR = delayed-release; ECMO = extracorporeal membrane oxygenation; EKG = electrocardiogram; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; Hb = hemoglobin; HF = heart failure; IFN-α = interferon alfa; IM = intramuscular; IR = immediate-release; IV = intravenous; LFT = liver function test; NS = normal saline; PK = pharmacokinetics; QT = interval between Q and T waves; QTc = QT interval corrected for heart rate; SCAR = severe cutaneous adverse reactions; SJS = Stevens-Johnson Syndrome; SMX = sulfamethoxazole; TDM = therapeutic drug monitoring; TMP = trimethoprim; XR = extended-release.

Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections

Updated: June 05, 2025
Reviewed: June 05, 2025

The potential exists for significant drug interactions and overlapping toxicities in children receiving medications for treatment or prevention of opportunistic infections (OIs). These children often receive other medications, including antiretrovirals, that interfere with the metabolism or elimination of OI medications. In particular, protease inhibitors and non-nucleoside reverse transcriptase inhibitors affect the cytochrome P450 or other transporter systems and may be associated with clinically significant drug interactions. The integrase strand transfer inhibitors cabotegravir and raltegravir are primarily metabolized by uridine diphosphate glucuronosyltransferase 1A1 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 the 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 data are available from studies involving adults with HIV, whereas data in children are extremely limited. New information continues to become available, and carefully reviewing each child's current medications, including prescription and over-the-counter medications, is important. Predicting the interaction potential is difficult when three or more drugs with similar metabolic pathways are coadministered, and significant interpatient variability amplifies these challenges. When possible, alternative agents with less drug interaction potential or use of therapeutic drug monitoring should be considered.

Drug Name	Toxicities	Recommendation
* The drug interactions included in this table were selected based on their potential clinical significance and are not inclusive of all potential drug interactions (see FDA Online Label Repository for complete information on drug interactions).		
Acyclovir	Overlapping Toxicities • Nephrotoxic drugs	Avoid other nephrotoxic drugs.
	Increased Concentrations (Both Drugs) and Overlapping Toxicities • *Antivirals*: valacyclovir, valganciclovir, ganciclovir, cidofovir • *ARVs:* tenofovir • *Immunosuppressive agents*: mycophenolate	Monitor for toxicities of these drugs.
Albendazole	Increased Albendazole Concentrations • *Anthelmintics*: praziquantel Decreased Albendazole Concentrations • *Anticonvulsants*: carbamazepine, phenobarbital, phenytoin • *Antivirals*: nirmatrelvir and ritonavir	Caution advised.
Amikacin	Overlapping Toxicities • *Antituberculars* (injectable): kanamycin, streptomycin • *Nephrotoxic or ototoxic drugs* • *Antimycobacterials*: capreomycin • ARVs: tenofovir • *Antivirals*: cidofovir	Caution advised. Avoid combining with cidofovir.
Amphotericin B Amphotericin B Lipid Complex Amphotericin B Liposome	Overlapping Toxicities • *Bone marrow suppressants*: corticosteroids • *Nephrotoxic drugs* • *Neuromuscular blockers*	Caution advised.

Drug Name	Toxicities	Recommendation
Artemether-Lumefantrine	Increased Drug Concentrations • *ARVs*: nevirapine	Monitor therapy when combined.
	Overlapping Toxicities • *ARVs*: PIs • *Antibacterials*: fluoroquinolones, macrolides • *Antifungals*: fluconazole, voriconazole • *Antimalarials*: quinidine, quinine • *Psychotropics*: quetiapine, tricyclic antidepressants	Coadministration with fluconazole or voriconazole should be avoided. For all other drugs, coadministration should be avoided, if possible; monitor for toxicities (QT prolongation).
Atovaquone	Decreased Atovaquone Concentrations • *Antimycobacterials*: rifampin, rifabutin • *ARVs*: lopinavir/ritonavir, atazanavir/ritonavir • *Antibiotics*: doxycycline	Coadministration of atovaquone and rifampin or atovaquone and rifabutin should be avoided.
Azithromycin	Overlapping Toxicities • *Antimalarials*: artemether/lumefantrine, chloroquine, quinine	Caution advised. Increased risk of QT prolongation.
Bedaquiline	Overlapping Toxicities • QT-prolonging agents	Bedaquiline may enhance the QTc-prolonging effects. Avoid concomitant use.
	• *Fecal microbiota (live)* (oral and rectal)	Avoid concomitant use.
Caspofungin	Decreased Caspofungin Concentrations • *Anticonvulsants*: phenytoin • *Antimycobacterials*: rifampin • A*RVs*: efavirenz, nevirapine	Increase in dose of caspofungin is recommended when coadministered with CYP450 inducers.
Cidofovir	Overlapping Toxicities • *Antibacterials*: aminoglycosides • *Antivirals*: foscarnet • *ARVs*: tenofovir • *Nephrotoxic drugs*	Monitor for toxicities of these drugs. Prehydrate with IV normal saline and probenecid to avoid nephrotoxicity.

Drug Name	Toxicities	Recommendation
Ciprofloxacin	Decreased Ciprofloxacin Absorption • *ARVs*: didanosine • *Minerals*: ferrous sulfate, zinc • *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 • *Antimalarials*: artemether/lumefantrine, quinine • *Antibacterials:* clarithromycin	Caution advised.
	• *Fecal microbiota (live)* (oral and rectal)	Avoid concomitant use.
Clarithromycin	Increased Clarithromycin Concentrations • *ARVs:* atazanavir/ritonavir, lopinavir/ritonavir • *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.
	Increased Concomitant Drug Concentrations • *ARVs*: etravirine	Consider alternative ARV.
	Decreased Clarithromycin Concentrations • *ARVs*: efavirenz, etravirine, nevirapine • *Antimycobacterials*: rifampin, rifabutin (rifabutin concentrations also increased)	Consider switching to azithromycin, which has less potential for drug interaction. For concomitant use of rifabutin and clarithromycin, consider decreasing dose of rifabutin or switching to azithromycin.
	Overlapping Toxicities • *Fecal microbiota (live)* (oral/rectal)	Clarithromycin may reduce fecal microbiota (live) (rectal) effectiveness.
Clindamycin	Decreased Clindamycin Antibacterial Efficacy • *Antibacterials*: chloramphenicol, erythromycin Overlapping Toxicities • *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.

Drug Name	Toxicities	Recommendation
Cycloserine	Overlapping Toxicities • *Antimycobacterials*: ethionamide, isoniazid	Caution advised.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Dapsone	Decreased Dapsone Concentrations • *Antimycobacterials*: rifampin	Coadministration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
	Decreased Dapsone Absorption • *ARVs*: atazanavir, didanosine suspension • *Gastrointestinal drugs*: antacids	For coadministration with antacids or didanosine suspension, give dapsone 1 hour before or 4 hours after the other medication.
	Overlapping Toxicities • *Bone marrow suppressants* or drugs associated with hemolysis	Caution advised.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Doxycycline	Decreased Doxycycline Concentrations • *Anticonvulsants*: carbamazepine, phenytoin • *Antimycobacterials*: rifampin	Potential for decreased doxycycline efficacy. Monitor for therapeutic failure.
	Overlapping Toxicities • *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Erythromycin	Increased Concentrations of Erythromycin • *Antifungals*: itraconazole (itraconazole concentrations also increased) Increased Concomitant Drug Concentrations • *ARVs*: tenofovir	Monitor for toxicities of both drugs, potential for QT prolongation.
	Overlapping Toxicities • *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.

Drug Name	Toxicities	Recommendation
Ethambutol	Overlapping Toxicities • *Neurotoxic drugs*	Caution advised.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Ethionamide	Potential for Increased Toxicity Due to Overlapping Toxicity • *Neurotoxic drugs* • *Antimycobacterials*: cycloserine, isoniazid	Caution advised.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Fluconazole	Decreased Fluconazole Levels • *Anticonvulsants*: phenytoin • *Antimycobacterials:* rifampin • *ARVs*: rilpivirine	Monitor for efficacy. May need to increase fluconazole dose.
	Increases Concomitant Drug Concentrations • *ARVs*: etravirine, nevirapine, saquinavir, tipranavir	May need to decrease dose of saquinavir. Avoid tipranavir with high doses of fluconazole (maximum fluconazole dose in adults: 200 mg). Caution advised with etravirine.
	• *Antineoplastics*: venetoclax	Decrease venetoclax dose by at least 50% in children requiring concomitant treatment.
	• *Antimycobacterials*: rifabutin	May need to decrease dose of rifabutin.
	• *Statins*: atorvastatin, lovastatin, simvastatin	Do not coadminister with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins, such as fluvastatin, rosuvastatin, and pravastatin, are preferred, or discontinue statin during antifungal therapy.
Flucytosine	Increased Flucytosine Concentrations • *Nephrotoxic drugs* Overlapping Toxicities • *QT-prolonging drugs*	Caution advised. Dose adjustments with therapeutic drug monitoring recommended with impaired renal function.

Drug Name	Toxicities	Recommendation
Foscarnet	Overlapping Toxicities • *Antivirals*: cidofovir • *Anti-pneumocystis drugs*: pentamidine • *Nephrotoxic drugs*	Monitor for toxicities of these drugs.
Ganciclovir	Increased Ganciclovir Concentrations • *ARVs*: tenofovir (concentrations also increased)	Monitor for toxicities of these drugs.
	Increased Concomitant Drug Concentrations • *ARVs*: didanosine	Caution advised.
	Overlapping Toxicities • *Antibacterials*: imipenem-cilastatin • *ARVs*: zidovudine • *Bone marrow suppressants* • *Nephrotoxic drugs*	Caution advised. Increased risk of seizures with imipenem-cilastatin.
Isavuconazole	Increased Concomitant Drug Concentrations • *Antineoplastics*: venetoclax	Reduce venetoclax dose by at least 50% in children requiring concomitant treatment. Resume previous venetoclax dose two to three days after discontinuation of isavuconazole.
Isoniazid	Decreased Isoniazid Concentrations • *Corticosteroids*: glucocorticoids (e.g., prednisolone)	Use with caution.
	Decreased Isoniazid Absorption • *Gastrointestinal drugs*: antacids	Caution advised. Take ≥1 hour before aluminum-containing antacids.
	Increased Concomitant Drug Concentrations • *Sedatives/hypnotics*: diazepam	Caution advised.
	Decreased Concomitant Drug Concentrations • *Antifungals*: itraconazole, ketoconazole	Coadministration should be avoided, if possible.

Drug Name	Toxicities	Recommendation
	Overlapping Toxicities • *Antimycobacterials*: cycloserine, ethionamide, itraconazole • *Hepatotoxic drugs* • *Neurotoxic drugs*	Caution advised.
Itraconazole and Ketoconazole	Increased Azole Concentrations • *Antibacterials*: clarithromycin, ciprofloxacin, erythromycin • *ARVs*: PIs	Monitor for toxicities and monitor concentrations. Consider azithromycin instead of other macrolides. High doses of itraconazole are not recommended with PIs.
	Increased Concomitant Drug Concentrations • *ARVs*: etravirine, maraviroc, PIs	Caution advised. Monitor for toxicities. Decrease adult maraviroc dose to 150 mg twice daily.
	• *Statins*: atorvastatin, lovastatin, simvastatin	Do not coadminister with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, and pravastatin are preferred; alternatively, discontinue statin during antifungal therapy.
	• *Antibacterials:* clarithromycin, erythromycin	Consider switching to azithromycin, which has less potential for drug interaction.
	• *Sedatives/hypnotics*: alprazolam, diazepam, midazolam	Coadministration of midazolam and alprazolam should be avoided. Coadministration of diazepam should be avoided, if possible.
	• *Antimalarial:* quinidine	Coadministration of quinidine should be avoided. QT prolongation may occur.
	Decreased Azole Concentrations • *ARVs*: efavirenz, etravirine, nevirapine, rilpivirine	Monitor concentrations. Coadministration of efavirenz should be avoided if possible.
	• *Anticonvulsants*: carbamazepine, fosphenytoin	Monitor concentrations.
	• *Antimycobacterials*: isoniazid, rifabutin, rifampin, rifapentine	Coadministration with rifampin should be avoided. Coadministration with rifabutin should be avoided, if possible. Monitor for toxicities and monitor concentrations.

Drug Name	Toxicities	Recommendation
	Decreased Azole Absorption • *ARVs*: didanosine • *Gastrointestinal drugs*: antacids, anticholinergics/antispasmodics, histamine H2-receptor antagonists, omeprazole, sucralfate	Monitor concentrations.
Mefloquine	Decreased Mefloquine Concentrations • *Antimalarials*: quinine • *Antimycobacterials:* rifampin	Monitor for decreased mefloquine efficacy. Coadministration of rifampin should be avoided, if possible; use rifabutin instead.
	Decreased Concomitant Drug Concentrations • *ARVs*: ritonavir, possibly other PIs	Monitor for virologic failure of PI-containing ART regimen.
	Overlapping Toxicities • *Antimalarials*: quinine • *QT-prolonging drugs*	Avoid coadministration, if possible. Monitor for toxicities (EKG changes, cardiac arrest, and seizures with quinine). If coadministered with quinine, give mefloquine at least 12 hours after last dose of quinine.
Nitazoxanide	Increased Concomitant Drug Concentrations • *Anticonvulsants*: phenytoin	Potential for interaction with other medications that are highly protein-bound. Use with caution as interaction will increase concentrations of concomitant medication.
Pentamidine	Overlapping Toxicities • *Antivirals*: foscarnet	Coadministration should be avoided, if possible. Monitor for toxicities (hypocalcemia, QT prolongation).
	• *ARVs*: didanosine, PIs	Coadministration should be avoided, if possible. Monitor for toxicities (QT prolongation with PIs; pancreatitis for didanosine).
	• *Bone marrow suppressants*	Monitor for toxicities.
	• *Nephrotoxic drugs*	Monitor for toxicities.
	• *QT-prolonging drugs*	Monitor for toxicities. Avoid coadministration, if possible.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.

Drug Name	Toxicities	Recommendation
Posaconazole	Decreased Posaconazole Drug Concentrations • *ARVs*: efavirenz, fosamprenavir, rilpivirine	Coadministration of fosamprenavir should be avoided. Coadministration of efavirenz should be avoided, if possible. If coadministered, monitor posaconazole concentrations and adjust dose accordingly.
	• *Anticonvulsants*: phenytoin	Coadministration should be avoided, if possible. If coadministered, monitor posaconazole concentrations and adjust dose accordingly.
	• *Antimycobacterials*: rifabutin, rifampin	Coadministration should be avoided, if possible. If coadministered, monitor posaconazole concentrations and adjust dose accordingly.
	Increased Concomitant Drug Concentrations • *ARVs*: atazanavir, etravirine, lopinavir, ritonavir, saquinavir	Coadministration should be avoided, if possible. Monitor for toxicities. Consider monitoring concentrations and adjust dose as necessary.
	• *Antibacterials*: clarithromycin, erythromycin	Coadministration should be avoided.
	• *Anticonvulsants*: phenytoin	Coadministration should be avoided.
	• *Sedatives/hypnotics*: alprazolam, diazepam, midazolam	Coadministration should be avoided, if possible. Monitor for toxicities.
	• *Antimycobacterials*: rifabutin	Coadministration should be avoided.
	• *Statins*: atorvastatin, lovastatin, simvastatin • *Antineoplastics*: venetoclax • *Immunosuppressives*: sirolimus, tacrolimus	Do not coadminister with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, and pravastatin are preferred; alternatively, discontinue statin during antifungal therapy.
	• *Antimalarials*: halofantrine, lumefantrine, mefloquine, quinidine, quinine	Coadministration should be avoided.
	Decreased Concomitant Drug Concentrations • *ARVs*: fosamprenavir	Coadministration should be avoided.
	• *QT-prolonging drugs*	Use with caution. Monitor for toxicities.

Drug Name	Toxicities	Recommendation
Proguanil	Decreased Proguanil Concentrations • *ARVs*: Atazanavir/ritonavir, efavirenz, lopinavir/ritonavir	Use with caution.
Pyrazinamide	Overlapping Toxicities • *Antimycobacterials*: ethionamide, rifampin • *Hepatotoxic drugs*	Use with caution. Monitor for hepatotoxicity.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Quinidine	Increased Quinidine Concentrations • *ARVs*: PIs	Coadministration of PIs should be avoided. Increased risk of arrhythmia. Coadministration may be necessary in the presence of life-threatening, severe malaria and in the absence of other therapy, while artesunate is obtained from the CDC.
	• *Antifungals*: itraconazole, posaconazole, voriconazole	Coadministration should be avoided. Increased risk of arrhythmia.
	Decreased Quinidine Concentrations • *ARVs*: etravirine	Use with caution. Monitor quinidine levels.
	Increased Concomitant Drug Concentrations • *Tricyclic antidepressants*	Coadministration should be avoided, if possible. Monitor for toxicities.
	Overlapping Toxicities • *QT-prolonging drugs*	Coadministration should be avoided, if possible. Monitor for toxicities (QT prolongation).
Ribavirin	Increased Concomitant Drug Concentrations • *ARVs*: didanosine	Coadministration should be avoided. Potential for increased risk of pancreatitis and mitochondrial toxicity.
	Decreased Concomitant Drug Concentrations • *ARVs*: stavudine, zidovudine	Coadministration should be avoided, if possible.
	Overlapping Toxicities • *ARVs*: zidovudine, all NRTIs	Coadministration should be avoided, if possible. Monitor for toxicities (anemia for zidovudine, lactic acidosis for all NRTIs).

Drug Name	Toxicities	Recommendation
Rifabutin	Increased Rifabutin Concentrations • *ARVs*: cobicistat, PIs	Use with caution. Monitor for rifabutin toxicity. Reduce rifabutin dose if coadministered with PIs.
	• Fluconazole	Use with caution. Monitor for rifabutin toxicity. Consider rifabutin dose reduction.
	• Voriconazole, itraconazole, posaconazole	Coadministration should be avoided, if possible. If coadministered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy).
	• *Antibacterials*: clarithromycin	Coadministration should be avoided, if possible. Monitor for rifabutin toxicity. Consider rifabutin dose reduction or using azithromycin instead.
	Increased Concomitant Drug Concentrations • *ARVs*: didanosine	Use with caution. Monitor for didanosine toxicity.
	Decreased Rifabutin Concentrations • *ARVs*: efavirenz, etravirine	Use with caution. Higher rifabutin dose required with efavirenz. Consider TDM.
	Decreased Concomitant Drug Concentrations • *ARVs*: rilpivirine, bictegravir, cabotegravir, dolutegravir, raltegravir, lenacapavir	Coadministration should be avoided.
	• *ARVs*: etravirine, maraviroc, saquinavir	Coadministration should be avoided, if possible.
	• *Antibacterials*: atovaquone, dapsone	Use with caution. Monitor for dapsone treatment failure.
	• *Antifungals*: azoles (except for fluconazole)	Coadministration should be avoided, if possible. If coadministered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy).
	• *Contraceptives*: oral	Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended.

Drug Name	Toxicities	Recommendation
Rifampin	Decreased Concomitant Drug Concentrations • *Contraceptives*: oral	Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended.
	• *ARVs*: PIs ± ritonavir, nevirapine, bictegravir, cabotegravir, dolutegravir, raltegravir, rilpivirine, maraviroc, cobicistat, zidovudine, lenacapavir	Significantly decreases exposure of ARVs; coadministration should be avoided if possible. Nevirapine: use only if other options are not available and close virologic and immunologic monitoring can be done; consider efavirenz instead. Raltegravir and dolutegravir dose increases may be required.
	• *Antimicrobials*: atovaquone, clarithromycin, dapsone, doxycycline	Coadministration 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.
	• *Antifungals*: azoles, caspofungin	Increase in dose of caspofungin is recommended when coadministered with CYP450 inducers. Monitor azoles for efficacy. May need to increase azole dose.
	• *Other*: corticosteroids, methadone	Caution advised with corticosteroids (decreased efficacy). Monitor for efficacy and/or opiate withdrawal symptoms with methadone.
	Overlapping Toxicities • *Bone marrow suppressants* • *Hepatotoxic drugs*	Monitor for toxicities of these drugs.
Streptomycin	Overlapping Toxicities • *Nephrotoxic drugs* • *Neuromuscular blockers*	Monitor for toxicities of these drugs.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.

Drug Name	Toxicities	Recommendation
Trimethoprim-Sulfamethoxazole (TMP-SMX)	Overlapping Toxicities • *Folate antagonists* • *Bone marrow suppressants*	Monitor for toxicities of these drugs.
	• *Fecal microbiota (live)* (oral/rectal)	Avoid concomitant use.
Valacyclovir	Potential for Increased Concentrations (of Both Drugs) and Overlapping Toxicities • *Antivirals*: acyclovir, cidofovir, ganciclovir, valganciclovir • *ARVs*: tenofovir, zidovudine	Monitor for toxicities of these drugs. Avoid other nephrotoxic drugs.
Valganciclovir	Potential for Increased Concentrations (of Both Drugs) and Overlapping Toxicities • *Antivirals*: acyclovir, cidofovir, ganciclovir, valacyclovir • *ARVs*: tenofovir, zidovudine	Monitor for toxicities of these drugs. Avoid other nephrotoxic drugs.
Voriconazole	Decreased Voriconazole Concentrations • *Anticonvulsants*: carbamazepine, long-acting barbiturates	Caution advised.
	• *Antimycobacterials*: rifabutin, rifampin	Rifabutin and rifampin coadministration should be avoided.
	• *ARVs*: efavirenz, nevirapine, ritonavir-boosted PIs	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. 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.
	Increased Voriconazole Concentrations • *ARVs*: etravirine (etravirine concentrations also increased)	Monitor voriconazole concentrations to reduce toxicity.

Drug Name	Toxicities	Recommendation
	Increased Concomitant Drug Concentrations • *Antimycobacterials*: rifabutin	Caution advised.
	• *ARVs*: ritonavir-boosted PIs, efavirenz	Caution advised.
	• *Statins*: atorvastatin, lovastatin, simvastatin	Do not coadminister with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, and pravastatin are preferred; alternatively, discontinue statin during antifungal therapy.
	• *Sedatives/hypnotics*: alprazolam, midazolam, triazolam	Coadministration should be avoided if possible. Monitor for toxicities.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CYP450 = cytochrome P450; EKG = electrocardiogram; FDA = U.S. Food and Drug Administration; IV = intravenous; NRTI = nucleoside reverse transcriptase inhibitors; PI = protease inhibitors; QT = interval between Q and T waves; QTc = QT interval corrected for heart rate; TDM = therapeutic drug monitoring

Figure 1. Recommended Immunization Schedule for Children and Adolescents With HIV Aged 0 Through 18 Years; United States, 2025

Immunization	Age																	
	Birth	1 mo.	2 mos.	4 mos.	6 mos.	9 mos.	12 mos.	13 mos.	15 mos.	18 mos.	19–23 mos.	2–3 yrs.	4–6 yrs.	7–10 yrs.	11–12 yrs.	13–15 yrs.	16 yrs.	17–18 yrs.
Respiratory syncytial virus (RSV-mAb [nirsevimab])	See notes.					See notes.												
Hepatitis B (HepB)	1st dose	2nd dose		See notes.	3rd dose													
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See notes.													
Diphtheria, tetanus, and acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose				4th dose				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See notes.		3rd or 4th dose; see notes.											
Pneumococcal conjugate (PCV15, PCV20)			1st dose	2nd dose	3rd dose		4th dose											
Inactivated poliovirus (IPV: <18 years)			1st dose	2nd dose	3rd dose								4th dose					See notes.
COVID-19 (2vCOV-mRNA, 1vCOV-aPS)					See notes.													
Influenza (IIV)					Annual vaccination, 1 or 2 doses									Annual vaccination, 1 dose only				
Influenza (LAIV)	Do not administer LAIV to children with HIV.																	
Measles, mumps, and rubella (MMR)					See notes.		See notes.			See notes.			See notes.	See notes.				
	Do not administer to severely immunocompromised children.																	
Varicella (VAR)							See notes.			See notes.			See notes.	See notes.				
	Do not administer to severely immunocompromised children.																	
Hepatitis A (HepA)					See notes.		2-dose series; see notes.											
Tetanus, diphtheria, and acellular pertussis (Tdap: ≥7 yrs)															1 dose			
Human papillomavirus (HPV)															See notes.			
Meningococcal (MenACWY-CRM: ≥2 mos; MenACWY-TT: ≥2 yrs)			2 or more primary doses, then boosters; schedule varies by minimum age and brand—see notes.															
Meningococcal B (MenB-4C, MenB-FHbp)															See notes.			
Respiratory syncytial virus (RSV [Abrysvo])															Seasonal administration during pregnancy; see notes.			
Pneumococcal polysaccharide (PPSV23)												See notes.						
Dengue (DEN4CYD: 9–16 yrs)														Seropositive in dengue-endemic areas only; see notes.				
	Do not administer to severely immunocompromised children.																	
Mpox																		See notes.


Legend
Range of recommended ages for vaccination
Catch-up immunization
Certain high-risk groups
Recommended vaccination based on shared clinical decision-making
Recommended vaccination can begin in this age group

Recommended Immunization Schedule for Children with HIV Aged 0 through 18 Years; United States, 2025

Updated: June 05, 2025
Reviewed: June 05, 2025

This schedule summarizes recommendations for administration of vaccines for children and adolescents with HIV aged 0 through 18 years and indicates the recommended ages for vaccine administration in this population for childhood and adolescent 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 U.S. Food and Drug Administration for that dose of the series. The combination measles, mumps, rubella, and varicella (MMRV) vaccine is an exception; in many circumstances, the measles, mumps, and rubella (MMR) vaccine and the varicella vaccine (VAR) should be administered to people with immunocompetent HIV, but the MMRV combination is **contraindicated** in immunocompetent HIV. Providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available on the VAERS website or by telephone at 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 infants exposed to HIV after 4 weeks of age if they have received proper post-exposure HIV testing and prophylaxis (see the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection: Diagnosis of HIV Infection in Infants and Children* and the *Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States*).

Respiratory Syncytial Virus Immunization (Nirsevimab)

Minimum Age: Birth

- A dose of nirsevimab should be administered to all infants through 7 months of age during or preceding the first respiratory syncytial virus (RSV) season.
- A dose of nirsevimab should be administered during or preceding the second RSV season to infants aged 8 months through 19 months with the following risk factors:
    - Children with severe immunocompromise (including that caused by HIV)
    - Children with chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season
    - Children with cystic fibrosis who have either: (1) manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable); or (2) weight-for-length less than 10th percentile

- American Indian/Alaska Native children

Hepatitis B Vaccine (HepB)

Minimum Age: Birth

- For routine vaccination and catch-up vaccination guidance, refer to the Centers for Disease Control and Prevention (CDC) hepatitis B vaccination notes.

Special Situations

- Infants born to hepatitis B surface antigen (HBsAg)–positive mothers and who have completed at least three doses of a licensed HepB series should be tested for HBsAg and the antibody to HBsAg (anti-HBs) at ages 9 months through 12 months (generally at the next well-child visit). Infants who are less than 2,000 grams at birth and receive a birth dose should receive four doses of HepB vaccine.
- 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.
- 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 CDC's Prevention of Hepatitis B Virus Infection in the United States; Recommendations of the Advisory Committee on Immunization Practices).

Rotavirus Vaccine (RV)

Minimum Age: 6 Weeks

- Limited safety and efficacy data are available for the administration of RV to infants who are potentially immunocompromised, including those with HIV. HIV is considered a precaution to rotavirus vaccination. In general, the following considerations support vaccination of infants with or exposed to HIV:
  - Vaccine strains of rotavirus are considerably attenuated.
  - Although an HIV diagnosis may not be established before the age of the first RV dose in infants born to mothers with HIV, ≤2% of infants with perinatal HIV exposure in the United States will eventually be determined to have HIV.
- RV can be administered to infants with HIV irrespective of CD4 T lymphocyte (CD4) cell 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 RV is administered at ages 2 months and 4 months, a dose at age 6 months is not indicated.

Diphtheria, Tetanus, and Acellular Pertussis Vaccine (DTaP)

Minimum Age: 6 Weeks

- DTaP is recommended at ages 2 months, 4 months, 6 months, and 15 months through 18 months, and ages 4 years 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.

Haemophilus influenzae Type B (Hib) Conjugate Vaccine

Minimum Age: 6 Weeks

- If PRP-OMP (PedvaxHIB) is administered at ages 2 months 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 individuals aged 5 years through 18 years if they are considered unvaccinated. "Unvaccinated" means meeting both criteria: (1) no doses received after 14 months of age and (2) no primary series and booster dose received.

Pneumococcal Conjugate Vaccine (15-valent) (PCV15) and (20-valent) (PCV20) and Pneumococcal Polysaccharide Vaccine (23-valent) (PPSV23)

Minimum Age: 6 Weeks for PCV15 or PCV20; 2 Years for PPSV23

- For routine dosing with pneumococcal conjugate vaccine, either PCV15 or PCV20 should be administered at 2 months, 4 months, 6 months, and 12 to 15 months. If PCV15 is chosen, at 2 years of age the child can receive a dose of PCV20 or PPSV23. This dose should be administered at least 8 weeks after PCV15. If PPSV23 was chosen the child should receive either PCV20 8 weeks after the dose of PPSV23 or another dose of PPSV23 5 years after the first dose of PPSV23.
- For catch-up dosing of children who received a partial series of PCV, catch-up should occur through 71 months of age. Either PCV15 or PCV20 can be used. At 2 years of age, if catch-up doses did NOT include a dose of PCV20, then a dose of PCV20 or PPSV23 is recommended. This dose should be administered at least 8 weeks after the dose of PCV15. If PPSV23 is chosen, it should be followed by either a dose of PCV20 8 weeks after the dose of PPSV23 or a second dose of PPSV23 5 years after the first dose of PPSV23.
- For children 6 years through 18 years of age who have not received any dose of PCV13, PCV15, or PCV20, either a dose of PCV20 or a dose of PCV15 followed by a dose of PPSV23 8 weeks later should be administered.

Inactivated Poliovirus Vaccine (IPV)

Minimum Age: 6 Weeks

- If four or more doses are administered prior to age 4 years, an additional dose should be administered between ages 4 years and 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.
- For catch-up dosing of adolescents aged 18 years who are suspected to have received either a partial series or no doses of IPV, the remaining doses should be administered to complete a three-dose primary series.
- For adolescents aged 18 years who completed the primary series and are at increased risk of exposure to poliovirus, one lifetime booster may be administered.

COVID-19 Vaccine (2vCOV-mRNA, 1vCOV-aPS)

Minimum Age: 6 Months

- People 6 months of age or older with immunosuppressive HIV are recommended for a primary series of 2024–2025 COVID-19 vaccine. The primary series consists of three doses. If Moderna is chosen, the interval between doses is 4 weeks. If Pfizer is chosen, the interval between dose 1 and dose 2 is 3 weeks, and the interval between dose 2 and dose 3 is 8 weeks. Doses of non-2024–2025 COVID-19 vaccine count toward the three-dose primary series.
- After the primary series, a booster dose of 2024–2025 COVID-19 vaccine is recommended at least 8 weeks after the final dose of the primary series. Additional doses may be given at 2-month intervals thereafter.
- For those aged ≥12 years who have a contraindication to mRNA vaccination or who refuse mRNA vaccination, Novavax (1vCOV-aPS), derived from the ancestral SARS-CoV-2 strain, is authorized for a two-dose primary series and one (and only one) booster dose (note: previous doses of mRNA vaccine count toward primary series doses).

Inactivated Influenza Vaccine (IIV)

Minimum Age: 6 Months for Inactivated Influenza Vaccine

- IIV is recommended for children with HIV. Administer annually to children with HIV aged 6 months through 18 years and to all their eligible close contacts (including household members).
- ACIP recommends that trivalent and quadrivalent live attenuated influenza vaccine (LAIV3 and LAIV4) not be used for children with HIV because of the uncertain but biologically plausible risk for disease attributable to the live vaccine virus (see Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 Influenza Season and Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2024–25 Influenza Season).
- Regardless of HIV status, ACIP recommends that children younger than 9 years of age who have not received two doses of influenza vaccine prior to the current season receive two doses (administered ≥4 weeks apart). Children who turn nine years old in the current season and who received one prior dose of influenza vaccine in the current season when they were 8 years old are recommended for a second dose in the current season.

Measles, Mumps, and Rubella Vaccine (MMR)

Minimum Age: 12 Months

- Two doses of MMR vaccine are recommended for all people with HIV aged ≥12 months who do not have evidence of current severe immunosuppression as defined by ACIP (see CDC's Child

and Adolescent Immunization Schedule and Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps).

  - Absence of severe immunosuppression is defined as CD4 percentages ≥15% for ≥6 months for people aged ≤5 years and CD4 percentages ≥15% and CD4 count ≥200 lymphocytes/mm^3 for ≥6 months for people aged >5 years.
  - When only CD4 counts or CD4 percentages are available for those aged >5 years, the assessment of severe immunosuppression can be on the basis of the CD4 values (count or percentage) that are available.
  - When CD4 percentages are not available for those aged ≤5 years, the assessment of severe immunosuppression can be on the basis of age-specific CD4 counts at the time CD4 counts were measured (i.e., absence of severe immunosuppression is defined as ≥6 months above age-specific CD4 count criteria: CD4 count >750 lymphocytes/mm^3 while aged ≤12 months and CD4 count ≥500 lymphocytes/mm^3 while aged 1 through 5 years).

- The first dose should be administered at age 12 months through 15 months, and the second dose should be administered at age 4 years through 6 years (or as early as 28 days after the first dose).
- Individuals with perinatally acquired HIV who were vaccinated prior to the establishment of effective antiretroviral therapy (ART) should receive two appropriately spaced doses (28 days between each dose) of MMR vaccine once effective ART has been established and there is no evidence of current severe immunosuppression, as defined by ACIP.
- MMR vaccine is recommended for international travelers aged 6 months through 11 months.
- The MMR and MMRV vaccines are **contraindicated** in people with AIDS or HIV who have severe immunosuppression with a CD4 count <200 cells/mm^3 or a CD4 percentage <15%.
- MMRV vaccine has not been studied in people with HIV and should not be substituted for MMR vaccine in people with HIV, regardless of CD4 count.

Varicella Vaccine (VAR)

Minimum Age: 12 Months

- Limited data are available on the safety and immunogenicity of VAR vaccine in children with HIV aged 1 year through 8 years in CDC immunologic categories 1 and 2 (CD4 percentages ≥15%) and clinical categories N, A, and B.
- Single-antigen VAR vaccine should be administered at the times indicated in the vaccine schedule to children and adolescents with HIV with CD4 percentages ≥15% of total lymphocytes and CD4 count ≥200 cells/mm^3.

  - If only CD4 percentages are available, single-antigen VAR vaccine should be considered for children and adolescents with HIV with CD4 percentages ≥15% of total lymphocytes.
  - If only CD4 counts are available, VAR vaccine should be administered to children aged 1 year through 5 years with CD4 counts ≥500 cells/mm^3, and VAR vaccine should be administered when indicated by the schedule to children aged ≥6 years with CD4 counts ≥200 cells/mm^3.

- Eligible children should receive two doses 3 months apart.
- Quadrivalent MMRV vaccine has not been studied in children or adolescents with HIV and should not be substituted for single-antigen VAR vaccine. The quadrivalent MMRV vaccine is **contraindicated** for people with HIV, regardless of CD4 count.

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 should be vaccinated at subsequent well-child visits.
- Children and adolescents aged ≥24 months who were not previously vaccinated should receive the HepA vaccine.
- International travelers aged 6 months through 11 months are recommended for HepA vaccine if traveling internationally to areas endemic or epidemic for hepatitis A.

Tetanus, Diphtheria, 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 between 11 years and 12 years of age.
- Individuals aged 11 years through 18 years who have not received Tdap should receive a dose of the vaccine followed by a tetanus toxoid–containing vaccine (either Tdap or tetanus, diphtheria [Td]) booster every 10 years thereafter.
- Administer one dose of Tdap vaccine to pregnant girls and women during each pregnancy (during 27 through 36 weeks gestation and preferred at 27 through 31 weeks gestation) regardless of the time since prior Tdap or Td vaccination.

Human Papillomavirus Vaccine (HPV)

Minimum Age: 9 Years

Note: Because HPV is not a live virus vaccine, it can be administered to individuals who are immunosuppressed because of disease or medication, including those with HIV. However, the immune response and vaccine efficacy in immunosuppressed individuals may be less than in immunocompetent individuals.

- HPV vaccines must be administered in a three-dose series to children and adolescents with HIV.
- 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 years or 12 years. The vaccine is approved to start as early as age 9 years.
- HPV vaccine should be administered early, beginning at 9 years of age, for persons with a history of sexual abuse and assault. HPV vaccine can be administered to anyone beginning at 9 years of age.
- Administer the second dose 1 month 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 three-dose series at ages 13 years through 26 years if not previously vaccinated.

Meningococcal ACWY Conjugate Vaccines

Minimum Ages: 2 Months for Meningococcal Conjugate Vaccine (Menveo) (MenACWY-CRM);
2 Years for Meningococcal Conjugate Vaccine (MenQuadfi)(MenACWY-TT)
10 Years for Pentavalent Meningococcal Conjugate Vaccine (Penbraya)(MenABCWY)

- Menveo
    - Children who initiate vaccination at 8 weeks should be administered doses at 2 months, 4 months, 6 months, and 12 months of age.
    - Unvaccinated children who initiate vaccination at 7 months through 23 months should be administered two doses, with the second dose at least 12 weeks after the first dose *and* after the first birthday.
    - Children and adolescents aged ≥24 months who have not received a complete series should be administered two primary doses at least 8 weeks apart.
    - For all children and adolescents receiving a primary series, a booster dose is recommended 3 years after the second primary dose (for children who receive the second dose prior to their seventh birthday; otherwise, the interval to the first booster should be 5 years) and every 5 years after that.
- MenQuadfi
    - Children and adolescents who initiate vaccination at 2 years of age should be given two primary doses at least 8 weeks apart. A booster dose is recommended 3 years after the second primary dose (for children who receive the second dose prior to their seventh birthday; otherwise, the interval to the first booster should be 5 years) and every 5 years after that.
- Penbraya can be used in children 10 years old and older whenever both MenACWY and MenB are indicated and if at least 6 months have passed since the last dose of Penbraya.

Meningococcal B Vaccines

Minimum Ages: 16 Years for Serogroup B Meningococcal (MenB) Vaccines, Including Bexsero (MenB-4C) and Trumenba (MenB-FHbp);
10 Years for People With HIV Plus Another High-Risk Condition for MenB Vaccines, Including Bexsero (MenB-4C) and Trumenba (MenB-FHbp)

- HIV infection alone is not an indication for MenB vaccine. Providers can consider vaccination in children and adolescents ≥10 years based on individual risk. Adolescents and 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 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. Refer to CDC's Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 for further details.
- For booster doses among people with high-risk conditions, refer to CDC's Prevention and Control of Meningococcal Disease.

- Penbraya can be used whenever both MenACWY and MenB are indicated, and if at least 6 months have passed since the last dose of Penbraya.

Respiratory Syncytial Virus Vaccine (Abrysvo)

- Women who are pregnant at 32 weeks and 0 days through 36 weeks and 6 days gestation from September through January in most of the continental United States should be administered one dose of RSV vaccine (Abrysvo). Administer RSV vaccine regardless of previous RSV infection.
- Either maternal RSV vaccination or infant immunization with nirsevimab (RSV monoclonal antibody) is recommended to prevent respiratory syncytial virus lower respiratory tract infection in infants.

Dengue Vaccine (DEN4CYD)

Minimum Age: 9 Years

- Children and adolescents aged 9 years through 16 years who live in dengue-endemic areas **and** have laboratory confirmation of previous dengue infection should be administered a three-dose series at 0 months, 6 months, and 12 months.
- Endemic areas include Puerto Rico, American Samoa, U.S. Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue-endemic areas and prevaccination laboratory testing, see the CDC dengue webpage and CDC laboratory testing requirements.
- Dengue vaccine is **contraindicated** in anyone with a CD4 percentage <15% or a CD4 count <200 cells/mm^3. A CD4 percentage of ≥15% **and** a CD4 count of ≥200 cells/mm^3 is a precaution to administering dengue vaccine.

Mpox Vaccine

Minimum Age: 18 Years

- A two-dose series, 28 days apart, should be administered to individuals aged 18 years who have any of the following risk factors:
    - Persons who are gay, bisexual, and other men who have sex with men (MSM) who in the past 6 months have had: (1) a new diagnosis of at least one sexually transmitted infection; (2) more than one sex partner; (3) sex at a commercial sex venue; or (4) sex in association with a large public event in a geographic area where mpox transmission is occurring
    - Persons who are sexual partners of the person described above
    - Persons who anticipate experiencing any of the situations describe