Introduction

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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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