

Opportunistic Infections in Children Living with HIV Infection (CLHIV) in the Era of Combination Antiretroviral Therapy

In the era before development of potent ART regimens, OIs were the primary cause of death in children living with HIV (CLHIV).¹ Current ART 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.²⁻⁶

Despite this progress, prevention and treatment of OIs remain critical components of care for CLHIV. OIs continue to be the presenting symptom of HIV infection among children whose HIV-exposure status is unknown, usually because of lack of maternal antenatal HIV testing or unrecognized acquisition of HIV infection during adolescence. For infants and children with known HIV infection, barriers such as inadequate medical care, lack of availability of suppressive ART regimens in the face of extensive prior treatment and drug resistance, caregiver substance abuse or mental illness, and multifactorial adherence difficulties may hinder effective HIV treatment and put them at risk of OIs, even in the ART era. These same barriers may then impede provision of primary or secondary OI prophylaxis to children for whom such prophylaxis is indicated. In addition, concomitant OI prophylactic drugs may only exacerbate the existing difficulties in adhering to ART. Multiple drug-drug interactions between OI, ARV, and other compounds 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 living with HIV but also seen in CLHIV, 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 CLHIV remain important even in the ART era.

History of the Guidelines

In 1995, the U.S. Public Health Service (USPHS) and IDSA developed guidelines for preventing OIs in adults, adolescents, and children infected with HIV.⁶ These guidelines, developed for health-care providers and their patients living with HIV, were revised in 1997, 1999, and 2002.⁷⁻⁹ In 2001, NIH, IDSA, and CDC convened a working group to develop guidelines for treating HIV-associated OIs, with a goal of providing evidence-based guidelines on treatment and prophylaxis. In recognition of unique considerations for infants, children, and adolescents living 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 OI treatment guidelines were initially published in December 2004.¹⁰ In 2009, recommendations for preventing and treating OIs in CLHIV and children exposed to but not infected by HIV were updated and combined into one document; a similar document on preventing and treating OIs among adults living with HIV, prepared by a separate group of adult HIV and infectious disease specialists, was developed at the same time. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research (OAR) of NIH. For the 2013 document and updates since 2013, the Opportunistic Infections Working Group, again under the auspices of OAR, convened a panel of pediatric specialists with expertise in specific OIs. For each section, members of the Panel review the literature since the last publication of that section of prevention and treatment guidelines, confer over several months, and produce draft guidelines. These draft guidelines are revised based on review by the full Panel and review and approval by the core writing group members. The final version is further reviewed by OAR, experts at CDC, the HIVMA of IDSA, the PIDS, and AAP before final approval and publication.

These guidelines are a companion to the *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*.¹¹ Clinicians providing care for adolescents are advised to use the Adult and Adolescent guidelines for guidance on the care of post-pubertal adolescents (sexual maturity rating [SMR] IV and V) and to use the Pediatric guidelines for guidance on the care of adolescents at SMR III or lower.

Sexual Maturity Rating		
GIRLS		
Breast Development	Stage	Pubic Hair Growth
Prepubertal; nipple elevation only	1	Prepubertal; no pubic hair
Small, raised breast bud	2	Sparse growth of hair along labia
General enlargement of raising of breast and areola	3	Pigmentation, coarsening and curling, with an 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	Prepubertal; 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 shape genitalia	5	Adult type and quantity, spread to medial thighs
Source: Tanner JM. Growth at adolescence. Oxford: Blackwell Scientific Publications, 1962		

Treatment of OIs is an evolving science, and availability of new agents or clinical data on existing agents may change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated.

Because these guidelines target CLHIV and children exposed to but not infected by HIV in the United States, the opportunistic pathogens discussed are those common to the United States and do not include certain pathogens such as *Penicillium marneffe* that may be seen almost exclusively outside the United States, that are common but seldom cause chronic infection (e.g., chronic parvovirus B19 infection), or that have the same risk, disease course, and approach to prevention and treatment in all children regardless of HIV status (e.g., streptococcal pharyngitis). The document is organized to provide information about the epidemiology, clinical presentation, diagnosis, and treatment of each pathogen.

The tables at the end of this document summarize recommendations for dosing of medications used for treatment and prevention of OIs in children ([Tables 1–3](#)), drug preparation and toxicity information for children ([Table 4](#)), and drug-drug interactions ([Table 5](#)). Vaccination recommendations for HIV-infected children and adolescents are presented in [Figures 1](#) and [2](#) at the end of the document.

2013 Rating Scheme for Pediatric Opportunistic Infections Recommendations (Used for all sections last updated in 2013)

In 2013, recommendations were rated using the rating system noted in the 2013 Pediatric Opportunistic Infections Recommendations Rating Scheme below. This rating scheme includes 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 where a higher quality of evidence exists for adults compared to children.

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 outweighs the risks of not adhering to the recommendation more often than not 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, non-randomized 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 a drug is effective in ARV-naïve patients and data from a non-randomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

Quality of Evidence Rating II—Non-Randomized Clinical Trials or Observational Cohort Data. In the absence of large, well-designed, pediatric, non-randomized trials or observational data, adult data from high-quality non-randomized 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, non-randomized trials or observational cohorts in children. Quality of Evidence Rating II* will be used if there are well-designed, non-randomized trials or observational cohort studies in adults with supporting and consistent information from smaller non-randomized 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 cell 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.

Pediatric Opportunistic Infections Recommendations Rating Scheme

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

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal 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, non-randomized trials or cohort studies with clinical outcomes, experts assigned a rating of I* or II*, respectively, if they judged the evidence from children sufficient to support findings from adult studies. In circumstances where there is level I or level II evidence from studies in adults with no or almost no accompanying data in children, experts assigned a rating of III.

Modified GRADE Process for Evidence Review and Recommendation Formulation and Rating

Beginning in 2015, the Pediatric OI Guidelines adopted a “modified GRADE” approach for the evidence review and formulation of recommendations to make the process more systematic and transparent and to be responsive to requests from our endorsing organizations to have a more systematic, standardized approach.

For more background about guidelines development from IDSA, see the [IDSA Handbook on Clinical Practice Guideline Development](#).

(A) Modified Grade Process for Evidence Review for Pediatric OI Guideline Recommendations

- Expert authors make a list of recommendations/topics to consider for recommendations in the revision.***
- 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 infection with [intervention] intravenous immune globulin (IVIG), [comparison] compared to no IVIG, prevent [outcomes] serious bacterial infections or death?
- 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 infection, 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 4 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 1 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 sub-population variability and exceptions are noted in the recommendations.

Note: For strong recommendations, 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 infection, 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, non-controversial 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 infection, 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*: [*NOTE: Search terms can be placed at top of document, instead of in individual tables, if they apply to all of the evidence tables in your section.]							
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.

(B) Organization & 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

4. Reference list

References

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10. Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40 Suppl 1:S1-84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15655768>.
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