Introduction

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The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (Pediatric Guidelines) address the diagnosis of HIV infection in infants and children and the use of antiretroviral therapy (ART) in children with HIV, including adolescents with sexual maturity ratings (SMRs, formerly Tanner staging) 1 to 3. Note that the guidelines developed by the Panel on Antiretroviral Guidelines for Adults and Adolescents are suitable for the care and management of adolescents in late puberty (SMRs 4–5).

The Pediatric Guidelines also include recommendations for managing adverse events that are associated with the use of antiretroviral (ARV) drugs in children and a detailed review of information about the safety, efficacy, and pharmacokinetics (PKs) of ARV agents in children. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data on an ongoing basis and regularly updates the guidelines. The guidelines are available on the Clinical Info website.

The Clinical Info website also provides separate guidelines for the following:

- The prevention and treatment of opportunistic infections (OIs) in children who were exposed to HIV and children with HIV infection[1];
- The use of ARV drugs in adolescents and adults with HIV[2];
- The use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States[3];
- The prevention and treatment of OIs in adolescents and adults with HIV[4]; *and*
- Other federally approved medical practice guidelines for HIV/AIDS are available, including HIV Counseling, Testing, and Referral; Hormonal Contraception; Laboratory Testing; Prevention with Persons with HIV; Occupational Postexposure Prophylaxis (PEP); Nonoccupational Postexposure Prophylaxis (nPEP); Pre-exposure Prophylaxis (PrEP); and Caring for Persons with HIV in Disaster Areas. In 2020, Guidance for COVID-19 and Persons with HIV was added.

These guidelines are developed for the United States and may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings.

The Pediatric Guidelines and the Perinatal Guidelines contain some closely related content that can overlap. To ensure that information is consistent across the guidelines and that users can easily find the information they need, the Panels that publish these two sets of guidelines have developed a process to jointly produce sections for shared content areas. The development of these sections is led by a group composed of members from both Panels; the sections are discussed separately and voted on by each full Panel. Jointly produced sections include—

- Maternal HIV Testing and Identification of Perinatal HIV Exposure
- Diagnosis of HIV Infection in Infants and Children
- Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

Since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, The State University of New Jersey), advances in medical management have dramatically reduced both the number of new pediatric HIV infections and the morbidity and mortality in children with HIV in the United States. The widespread use of ARV drugs in people with HIV during pregnancy and the use of ARV prophylaxis in infants who have been exposed to HIV have reduced the annual rate of perinatally acquired HIV infection[5,6] from a peak of 43.1 per 100,000 births in 1992 to 0.8 per 100,000 births in 2019. Racial and ethnic disparities are evident in annual rates of new perinatal infection; in 2019, perinatal infections occurred in Black or African American infants (2.9 per 100,000 births) at annual rates of 5 and 10 times that of Hispanic/Latinx (0.6 per 100,000 births) and White infants (0.3 per 100,000 births), respectively.[5] Since the introduction of ART, mortality in children with perinatal HIV infection has decreased by about 90%, and the incidence of OIs and other infections in these children has significantly declined.[7,8] Children with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.[9-11] ARV drug-resistance testing has made it easier for clinicians to choose effective initial and subsequent regimens. Treatment strategies focus on timely initiation of ARV regimens that are capable of maximally suppressing viral replication, which can prevent disease progression, preserve or restore immunologic function, and prevent the development of drug resistance. In addition, the availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burden, and less frequent medication administration—all factors that can improve adherence and outcomes. However, delays in the development and testing of pediatric formulations continue to limit the availability of optimal ARV regimens for children, especially infants.[12]

Children with HIV in the United States are increasingly born outside the United States[13]; they may be members of immigrant families or they may have been adopted by U.S. residents. These children may have non-B subtypes of HIV, incomplete medical and treatment histories, an increased risk of tuberculosis and other infections that are endemic in their countries of origin, and legal and psychosocial needs related to immigration.

Finally, as children with HIV grow older, new challenges arise related to adherence, drug resistance, reproductive health planning, transition to adult medical care, and the potential for long-term complications from HIV and its treatments.[11,14,15]

The pathogenesis of HIV infection and the virologic and immunologic principles underlying the use of ART are generally similar for all individuals with HIV. However, unique considerations exist for infants, children, and adolescents with HIV, including—

- Acquisition of infection through perinatal exposure for most children with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection[16];
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- Age-specific interpretations of CD4 T lymphocyte (CD4) cell counts;
- Higher plasma viral loads in infants with perinatal HIV infection than in adolescents and adults with nonperinatal HIV infection;
- Age-related changes in PK parameters that are caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance[17];
- Differences in the clinical manifestations and treatment of HIV in growing, immunologically immature individuals; *and*

- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

The care of children with HIV is complex and evolves rapidly as results of new research are reported, new ARV drugs are approved, and new approaches to treatment are recommended. As new drugs become available, a critical need exists for clinical trials that define appropriate drug doses and identify possible toxicities in infants, children, and adolescents. As additional ARV drugs are approved and optimal strategies for the use of these drugs in children become better understood, the Panel will modify these guidelines.

The recommendations in these guidelines are based on the current state of knowledge regarding the use of ARV drugs in children. Evidence is drawn primarily from published data regarding the treatment of HIV in infants, children, adolescents, and adults; however, when no such data are available, unpublished data and the clinical expertise of the Panel members are also considered. These guidelines are only a starting point for medical decision-making and are not meant to supersede the judgment of clinicians who are experienced in the care of children with HIV. Because of the complexity of caring for children with HIV, health care providers with limited experience in the care of these patients should consult a pediatric HIV specialist. The HIV/AIDS Management Clinician Consultation Center is an excellent resource for telephone consultation. The Center can be contacted at 1-800-933-3413, 9 a.m. to 8 p.m. ET, Monday through Friday.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	The guidelines provide guidance to HIV care practitioners in the United States on the optimal use of antiretroviral (ARV) agents when treating infants, children, and adolescents in early to mid-puberty (sexual maturity rating [SMR] 1–3) with HIV.
Panel Members	The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) is composed of approximately 34 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection (e.g., parents and caregivers of children and youth with HIV). The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Paediatric and Perinatal HIV/AIDS Research Group and a representative from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine participate as nonvoting, *ex officio* members of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the panel roster.
Financial Disclosure	All members of the Panel submit an annual financial disclosure statement in writing, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infections. A list of the latest disclosures is available on the Clinical Info website.
Users of the Guidelines	Providers of care to infants, children, and adolescents with HIV in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of the Office of AIDS Research Advisory Council (OARAC)

Topic	Comment
Funding Source	Office of AIDS Research, NIH, and HRSA
Evidence Collection	A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel working groups. The recommendations generally are based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.
Recommendation Grading	Described in Table 2
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version that is acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on infants, children, and adolescents in early-to-mid-puberty (SMR 1–3) with HIV. Guidelines for the treatment of adolescents in late puberty (SMR 4–5) are provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of antiretroviral therapy (ART) in people who are pregnant or are trying to conceive (including maternal and infant interventions to prevent perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These and other HIV guidelines are also available on the Clinical Info website.
Update Plan	The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the Clinical Info website until the guidelines can be updated with appropriate changes. All sections of the guidelines are reviewed at least once a year, with updates as appropriate.
Public Comments	A 2-week public comment period follows the release of the updated guidelines on the Clinical Info website. The Panel reviews these comments to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at Contact Us

Basis for Recommendations

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.

When approving drugs for use in children, the FDA often extrapolates efficacy data from adult trials, in addition to using safety and PK data from studies in children. Because of this, recommendations for use of ARV drugs in children often rely, in part, on data from clinical trials or studies in adults. Because the course of HIV disease and the effects of ARV drugs in pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients, it is appropriate to base approval of ARV drugs for children on evidence from adequate and well-controlled investigations in adults if—

- Supplemental data exist on the PKs of the drug in children, indicating that systemic exposure in adults and children is similar; *and*
- Studies are provided that support the safety of using the drug in pediatric patients.[18-20]

If a concern exists that concentration–response relationships might be different in children than in adults, then pediatric drug approval should include evidence from studies that relate drug activity to drug levels (pharmacodynamic data) in children. In many cases, the evidence from studies on the use of ARV drugs in adults (especially from randomized clinical trials) is much more substantial and higher in quality than the available evidence from studies in children. Therefore, for pediatric recommendations, the following rationale has been used when the evidence from studies in children is limited or of lower quality:

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** pediatric data from well-designed, nonrandomized trials or observational cohort studies with 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 3 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

- 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 a clinical benefit to initiating treatment at a certain CD4 cell count, and data from smaller observational studies in children indicate that treatment initiation at a similar CD4 cell count is associated with clinical benefit.

Quality of Evidence Rating III—Expert Opinion

- The criteria do not differ for adults and children.

In an effort to improve the quality of evidence available to guide the management of HIV infection in children, clinicians are encouraged to discuss participation in trials with children and their caregivers. Information about clinical trials for adults and children with HIV can be obtained from the Clinical Info website or by telephone at 1-800-448-0440.

Table 2. Rating Scheme for Recommendations

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**[a] with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials **in adults** with clinical outcomes and/or validated laboratory endpoints, plus accompanying data **in children**[a] from one or more well-designed, nonrandomized trials or observational cohort studies with clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies **in children**[a] with clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies **in adults** with clinical outcomes, plus accompanying data **in children**[a] from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

[a] These are studies that include children or children and adolescents, but not studies that are limited to postpubertal adolescents.

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