



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Introduction (Last updated May 22, 2018; last reviewed May 22, 2018)

The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (Pediatric Guidelines) address the use of antiretroviral therapy (ART) for **children living with HIV, including adolescents** with sexual maturity rating (SMR, formerly Tanner staging) I to III (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 [SMR IV–V]**). Guidance on management of adverse events associated with use of antiretroviral (ARV) drugs in children and a detailed review of information about safety, efficacy, and pharmacokinetics (PK) of ARV agents in children is also included. 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 provides regular updates to the guidelines. The guidelines are available on the *AIDSinfo* website at <http://aidsinfo.nih.gov>.

The *AIDSinfo* website also includes separate guidelines for:

1. The prevention and treatment of opportunistic infections (OIs) in children exposed to HIV and children with HIV infection,¹
2. The use of ARV agents in adolescents and adults with HIV,²
3. The use of ARV drugs in pregnant women with HIV,³ *and*
4. The prevention and treatment of OIs in adolescents and adults with HIV.⁴

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 at <http://www.who.int/hiv/pub/arv/en>.

The Pediatric Guidelines and the Perinatal Guidelines contain content that is closely related and sometimes overlapping. To ensure that information is consistent across the guidelines and that users can easily find the information they need, the Panels of these two 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 authors 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 the HIV-Exposed Neonate**

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 living with HIV in the United States. The widespread use of ARV drugs in pregnant women living with HIV and ARV prophylaxis in HIV-exposed infants have together reduced vertical transmission rates to less than 2%, with fewer than 50 new infant infections estimated for the United States in 2014.**⁵ **Since the introduction of combination ART, mortality in children with perinatal HIV infection has decreased by more than 80% to 90%, and opportunistic and other related infections in children have significantly declined.**^{6,7} **Children living with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.**^{8,9} ARV drug-resistance testing has enhanced the ability to choose effective initial and subsequent regimens. Treatment strategies continue to focus on timely initiation of ART regimens that are capable of maximally suppressing viral replication to 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. Finally, as children living

with HIV grow older, there are new challenges 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.¹⁰⁻¹³

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

- Acquisition of infection through perinatal exposure for most children living with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection;¹⁴
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months old;
- Age-specific interpretation 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;
- Changes in PK parameters with age, caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;¹⁵
- 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 living 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, clinical trials are critically needed to define appropriate drug doses and identify possible toxicities in infants, children, and adolescents. As additional ARV drugs become approved and optimal strategies for 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 infection. Because of the complexity of caring for children living with HIV, and the decreasing number of children with perinatally acquired HIV in the United States, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist. **The HIV/AIDS Management Clinician Consultation Center is an excellent resource for phone consultation. They can be contacted at (800) 933-3413, 9 am to 8 pm EST, Monday through Friday.**¹⁶

Guidelines Development Process

An outline of the composition of the Panel and the guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	Provide guidance to HIV care practitioners on the optimal use of ARV agents in infants, children, and adolescents (through mid-puberty) living with HIV in the United States.
Panel Members	The Panel is composed of approximately 35 voting members who have expertise in 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 living with HIV). The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, <i>ex officio</i> member 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 for management of HIV infections. A list of the latest disclosures is available on the <i>AIDSinfo</i> website (http://aidsinfo.nih.gov).
Users of the Guidelines	Providers of care to infants, children, and adolescents living with HIV in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of OARAC
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 section working groups. The recommendations are generally 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 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	<p>These guidelines focus on infants, children, and adolescents in early puberty (SMR I–III) living with HIV. Guidance for treatment of adolescents in late puberty (SMR IV–V) is provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents.</p> <p>Separate guidelines outline the use of ART in pregnant women with HIV infection (including maternal and infant interventions for prevention of perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV infection, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the <i>AIDSinfo</i> website (http://www.aidsinfo.nih.gov).</p>
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 significant 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 <i>AIDSinfo</i> website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once a year.
Public Comments	A 2-week public comment period follows release of the updated guidelines on the <i>AIDSinfo</i> website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov .

Basis for Recommendations

Recommendations in these guidelines are based upon 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.

Because licensure of drugs in children often is based on extrapolation of efficacy data from adult trials in addition to safety and PK data from studies in children, recommendations for ARV drugs often rely, in part, on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if:

- The course of the disease and the effects of the drug in the pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients;
- Supplemental data exist on PKs of the drug in children, indicating that systemic exposure in adults and children are similar; and
- Studies are provided that support the safety of the drug in pediatric patients.¹⁷⁻¹⁹

Studies relating drug activity to drug levels (pharmacodynamic data) in children also should be available if there is a concern that concentration-response relationships might be different in children. In many cases, there is much more substantial and higher-quality evidence related to use of ARV drugs from studies (especially randomized clinical trials) in adults than 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 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 3 clinical trial in adults demonstrates that a drug is effective in ARV-naïve 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 clinical benefit to initiating treatment at a certain CD4 cell count and data from smaller observational studies in children indicate that 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 increase the amount and improve the quality of evidence available for guiding management of HIV infection in children, the discussion of available trials with children and their caregivers is encouraged. Information about clinical trials for adults and children with HIV infection can be obtained from the

AIDSinfo website (<https://aidsinfo.nih.gov/Clinical-Trials/>) or by telephone at (800) 448-0440.

Table 2. Rating Scheme for Recommendations

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

^a Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents

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