



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Introduction (Last updated March 1, 2016; last reviewed March 1, 2016)

These updated Guidelines for the Use of Antiretroviral Agents Pediatric HIV Infection address the use of antiretroviral therapy (ART) for HIV-infected infants, children, and adolescents. In general, these guidelines are appropriate for the care and management of youth with sexual maturity rating (SMR, formerly Tanner staging) I-III, whereas 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 HIV-Infected Children (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 the prevention and treatment of opportunistic infections (OIs) in HIV-exposed and -infected children,<sup>1</sup> for the use of ARV agents in HIV-infected adolescents and adults,<sup>2</sup> for the use of ARV drugs in pregnant HIV-infected women,<sup>3</sup> and for the prevention and treatment of OIs in HIV-infected adults.<sup>4</sup> These guidelines are developed for the United States and may not be applicable in other countries. The World Health Organization (WHO) provides guidelines for resource-limited settings at <http://www.who.int/hiv/pub/arv/en>.

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 morbidity and mortality in HIV-infected children in the United States. Mortality in children with perinatal HIV infection has decreased by more than 80% to 90% since the introduction of protease inhibitor-containing combinations and opportunistic and other related infections in children have significantly declined in the era of ART.<sup>5,6</sup> 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 capable of maximally suppressing viral replication in order to prevent disease progression, preserve or restore immunologic function, and reduce the development of drug resistance. At the same time, availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burdens, and less frequent medication administration, all factors that can improve adherence and outcomes. The use of ARV drugs in HIV-infected pregnant women has resulted in a dramatic decrease (to less than 2%) in the rate of HIV transmission to infants in the United States. In addition to decreasing the number of infants with HIV infection, children in the United States who are HIV-infected are less likely to develop AIDS because of routine and early institution of effective ART.<sup>7,8</sup> Finally, as a group, children living with HIV infection are growing older, bringing 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.<sup>9-11</sup>

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

- Acquisition of infection through perinatal exposure for most infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to ARV drugs in most perinatally infected children;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- Age-specific interpretation of CD4 T lymphocyte (CD4) cell counts;
- Higher viral loads in perinatally-infected infants than in HIV-infected adolescents and adults;

- Changes in PK parameters with age caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;<sup>12</sup>
- Differences in the clinical manifestations and treatment of HIV infection secondary to onset of infection in growing, immunologically immature individuals; and
- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

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 infection in infants, children, adolescents, and adults; however, when no such data were available, unpublished data and the clinical expertise of the Panel members were also considered. The Panel intends for these guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

## 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** (page 1 of 2)

Topic	Comment
<b>Goal of the Guidelines</b>	Provide guidance to HIV care practitioners on the optimal use of ARV agents in HIV-infected infants, children, and adolescents (through puberty) in the United States.
<b>Panel Members</b>	The Panel is composed of approximately 32 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. 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, ex officio member of the Panel. The US 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 <a href="#">Panel Roster</a> .
<b>Financial Disclosure</b>	All members of the Panel submit a financial disclosure statement in writing annually, 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 ( <a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a> ).
<b>Users of the Guidelines</b>	Providers of care to HIV-infected infants, children, and adolescents <b>in the United States</b>
<b>Developer</b>	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC
<b>Funding Source</b>	Office of AIDS Research, NIH and HRSA
<b>Evidence Collection</b>	A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the François-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
<b>Recommendation Grading</b>	Described in <a href="#">Table 2</a> .
<b>Method of Synthesizing Data</b>	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. <b>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.</b>

**Table 1. Outline of the Guidelines Development Process** (page 2 of 2)

<b>Topic</b>	<b>Comment</b>
<b>Other Guidelines</b>	<p>These guidelines focus on HIV-infected infants, children, and adolescents <b>in early puberty (SMR I-III)</b>. For more detailed discussion of issues of treatment for adolescents <b>in late puberty (SMR IV-V)</b>, the Panel defers to the expertise offered by the <a href="#">Panel on Antiretroviral Guidelines for Adults and Adolescents</a>.</p> <p>Separate guidelines outline the use of ART in HIV-infected pregnant women and interventions for prevention of perinatal transmission, ART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the <i>AIDSinfo</i> website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</p>
<b>Update Plan</b>	<p>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 yearly.</p>
<b>Public Comments</b>	<p>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 <a href="mailto:contactus@aidinfo.nih.gov">contactus@aidinfo.nih.gov</a>.</p>

### ***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:

1. 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;
2. Supplemental data exist on PKs of the drug in children indicating that systemic exposure in adults and children are similar; and
3. Studies are provided that support the safety of the drug in pediatric patients.<sup>13-15</sup>

Studies relating activity of the drug-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, evidence related to use of ARV drugs is substantially greater from adult studies (especially randomized clinical trials) than from pediatric studies. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

#### **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 III clinical trial in adults demonstrates 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 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 HIV-infected adults and children can be obtained from the AIDSinfo website (<http://aidsinfo.nih.gov/ClinicalTrials/>) or by telephone at 1-800-448-0440.

**Table 2. Rating Scheme for Recommendations**

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

<sup>a</sup> Studies that include children or children and adolescents, but not studies limited to postpubertal adolescents

## References

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