



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Introduction (Updated August 11, 2011)

These guidelines address issues specific to the use of antiretroviral therapy (ART) for HIV-infected infants, children, and adolescents (through puberty). Included is information on the management of adverse events of antiretroviral (ARV) drugs in children and details on pediatric data related to ARV agents. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data related to pediatric ART on an ongoing basis and provides regular updates to the guidelines. The guidelines are available on the *AIDSinfo* Web site at <http://aidsinfo.nih.gov>.

Separate sets of guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-exposed and -infected children¹ and for the use of ARV agents in HIV-infected postpubertal adolescents and adults² are also available on the *AIDSinfo* Web site. Because these guidelines are developed for the United States, they 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 development of the initial guidelines in 1993 (with the support of the François-Xavier Bagnoud Center [FXBC], University of Medicine and Dentistry of New Jersey [<http://www.fxbcenter.org>]), dramatic advances in medical management have followed the results of clinical trials of ARV combination therapies in children. HIV mortality has decreased by more than 80%–90% since the introduction of protease inhibitor (PI)-containing combinations, and opportunistic and other related infections have significantly decreased in the era of highly active antiretroviral therapy (HAART)³⁻⁹. Advances including resistance testing and the ability to measure ARV drug levels have enabled clinicians to more carefully choose very effective initial regimens while preserving selected drugs and drug classes for second- or third-line regimens. Therapeutic strategies continue to focus on early initiation of ARV regimens capable of maximally suppressing viral replication to prevent disease progression, preserve immunologic function, and reduce the development of resistance. At the same time, availability of new drugs and drug formulations has led to regimens with less frequent dosing schedules that improve adherence. Improved monitoring and dosing schedules have also led to a decrease in drug failure due to toxicity. The use of ART during pregnancy in HIV-infected women has resulted in a dramatic decrease in the transmission rate to infants, which is currently less than 2% in the United States, and the number of infants with AIDS in the United States continues to decline¹⁰⁻¹¹. Finally, children living with HIV infection are, as a group, growing older, bringing new challenges of adherence, drug resistance, **reproductive health planning**, management of multiple drugs, **and long-term complications from HIV and its treatments**.

Although the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of ART are similar for all HIV-infected people, 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 zidovudine and other 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 differences in CD4 cell counts;
- Changes in pharmacokinetic (PK) parameters with age caused by the continuing development

- Differences in the clinical and virologic manifestations of perinatal HIV infection secondary to the occurrence of primary infection in growing, immunologically immature persons; and
- Special considerations associated with adherence to ARV treatment for infants, children, and adolescents.

The recommendations in these guidelines represent the current state of knowledge regarding the use of ARV drugs in children and are based on published and unpublished data regarding the treatment of HIV infection in infants, children, adolescents, and adults and, when no definitive data were available, the clinical expertise of the Panel members. The Panel intends the 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 development 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 antiretroviral (ARV) agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States. |
| Panel members | The Panel is composed of approximately 25 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. The Panel also includes at least 1 representative from each of the following Health and Human Services (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 U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected by the Panel 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 on the panel roster . |
| Financial disclosure | All members of the Panel submit a written financial disclosure 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> Web site (http://aidsinfo.nih.gov). |
| Users of the guidelines | Providers of care to HIV-infected infants, children, and adolescents |
| Funding source | Office of AIDS Research, NIH |
| Evidence collection | The recommendations in these guidelines 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. |
| Recommendation grading | Described in Table 2 . |

| Topic | Comment |
|------------------------------------|--|
| 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 and votes on all proposals during monthly teleconferences. Proposals receiving endorsement from a consensus of members are included in the guidelines as official Panel recommendations. |
| Other guidelines | <p>These guidelines focus on HIV-infected infants, children, and adolescents through puberty. Separate guidelines outline the use of antiretroviral therapy (ART) in pregnant HIV-infected women and interventions for prevention of mother-to-child transmission (PMTCT), ART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. The guidelines described are also available on the <i>AIDSinfo</i> Web site (http://www.aidsinfo.nih.gov).</p> <p>These guidelines focus on HIV-infected children from infancy through puberty. For more detailed discussion of issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents.</p> |
| Update plan | The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates to the guidelines 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 accompanying recommendations on the <i>AIDSinfo</i> Web site until the guidelines can be updated with appropriate changes. |
| Public comments | A 2-week public comment period follows release of the updated guidelines on the <i>AIDSinfo</i> Web site. 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@aidinfo.nih.gov . |

Table 1. Outline of the Guidelines Development Process

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 relies on efficacy data from adult trials in addition to safety and PK data in children, recommendations for ARV drugs may need to rely 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) it is expected that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations 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 supporting the safety of the drug in pediatric patients are provided¹².

In addition, if there was a concern that concentration-response relationships may be different in children, studies relating activity of the drug to drug levels (pharmacodynamic data) in children should be available.

In many cases, there is substantially greater evidence related to use of ARV drugs 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.**

In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.

- 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. For example, if 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, a rating of I* may be used for quality of evidence.

- **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 may be used if there are sufficient pediatric data consistent with high-quality 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. For example, if a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 cell count and observational data in children indicate that a similar CD4 count is associated with clinical outcomes in children older than a specific age, a rating of II* may be used for quality of evidence.

- **Quality of Evidence Rating III—Expert opinion.**

The criteria do not differ for adults and children.

Table 2. Rating Scheme for Recommendations

| 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, nonrandomized trials or observational cohort studies <u>in children</u>[†] with long-term clinical outcomes</p> <p>II*: One or more well-designed, nonrandomized 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> |
| <p>[†]Studies that include children or children/adolescents but not studies limited to postpubertal adolescents</p> | |

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

The following concepts were considered in the formulation of these guidelines.

- Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States¹³. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*
- The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all ARV drugs produced.
- Although some information regarding the efficacy of ARV drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of Phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved ARV drug in children.
- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a

* In areas where enrollment in clinical trials is possible, enrolling the child in available trials should be discussed with the caregivers of the child. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDSinfo Web site (<http://aidsinfo.nih.gov/ClinicalTrials/>) or by telephone at 1-800-448-0440.

specialist in pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted.

- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families requires a multidisciplinary team approach that includes physicians, nurses, nutritionists, pharmacists, dentists, psychologists, social workers, **child life specialists**, and outreach workers.
- Health care providers considering ART for infants, children, or adolescents should consider certain factors influencing adherence to therapy, including:
 - availability and palatability of drug formulations;
 - impact of the medication schedule—including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food—on quality of life;
 - ability of the child’s caregiver or the adolescent to administer complex drug regimens and availability of resources that might be effective in facilitating adherence; and
 - potential for drug interactions.
- The choice of initial ARV regimen should include consideration of factors that may limit future treatment options, such as the presence of or potential for the development of resistance to ARV drugs. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition are all essential in the care of HIV-infected children because they may significantly influence quality of life.

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