Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Introduction (Last updated November 1, 2012; last reviewed November 1, 2012)

These guidelines address the use of antiretroviral therapy (ART) for HIV-infected infants, children, and adolescents (through puberty). Included is information on management of adverse events associated with use 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 on an ongoing basis and provides regular updates to the guidelines. The guidelines are available on the AIDS*info* website at http://aidsinfo.nih.gov.

Also available on the AIDS*info* website are separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children[1] and for the use of ARV agents in HIV-infected (postpubertal) adolescents and adults.[2] 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.

Advances in medical management, based on results of clinical trials of ARV combination therapies in children, have dramatically reduced morbidity and mortality in HIV-infected children in the United States since the guidelines were first developed in 1993 (with the support of the Francois-Xavier Bagnoud Center, University of Medicine and Dentistry of New Jersey). HIV mortality has decreased by more than 80% to 90% since the introduction of protease inhibitor (PI)-containing combinations and opportunistic and other related infections have significantly declined in the era of ART.[3, 4] Resistance testing has enhanced the ability to choose very effective initial regimens while preserving selected drugs and drug classes for second- or third-line regimens. Therapeutic strategies continue to focus on timely 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 more potent regimens with lower toxicity, lower pill burdens, and less frequent medication administration, all factors which are associated with better adherence and outcomes. The use of ARV drugs during pregnancy in HIV-infected women has resulted in a dramatic decrease in the rate of HIV transmission to infants in the United States, to less than 2%. The number of infants with AIDS in the United States continues to decline because of the low rate of new infant infections and the availability of ART to prevent AIDS in HIV-infected infants.[5, 6] Finally, as a group, children living with HIV infection are growing older, bringing new challenges related to adherence, drug resistance, reproductive health planning, management of multiple drugs, and potential for long-term complications from HIV and its treatments.

The pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of ART are similar for all HIV-infected people, 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 age 18 months;
- Age-specific differences in interpreting CD4 T lymphocyte (CD4 cell) counts;
- Changes in pharmacokinetic (PK) parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
- 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.

These recommendations 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, on 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

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 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 Department of 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 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 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 AIDS*info* website (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected infants, children, and adolescents
Developer	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC
Funding source	Office of AIDS Research, NIH and Health Resources and Services Administration
Evidence collection	A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the Francois-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.
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 and votes on all proposals during monthly teleconferences. Proposals endorsed by a consensus of members are included in the guidelines as official Panel recommendations.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process, cont'd

Topic	Comment
Other guidelines	These guidelines focus on HIV-infected infants, children, and adolescents 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. Separate guidelines outline the use of antiretroviral therapy (ART) in HIV-infected pregnant 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. These guidelines are also available on the AIDS*info* website (http://aidsinfo.nih.gov).
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. 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 AIDS*info* website 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 AIDS*info* 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 efficacy data from adult trials in addition to safety and PK data in children, recommendations for ARV drugs may need to 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.[7]

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.**
  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. 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.** 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. 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.** The criteria do not differ for adults and children.

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† 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† from one or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, non-randomized trials or observational cohort studies in children† with long-term clinical outcomes **II*:** One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children† from one or more smaller non-randomized trials or cohort studies with clinical outcome data **III:** Expert opinion

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

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 States.[8] Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy to both infected women and their infants and to reducing 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 collaborating to ensure that drug formulations suitable for administration to infants and children are available for all ARV drugs produced.
- Some information about the efficacy of ARV drugs for children can be extrapolated from clinical trials involving adults, but concurrent clinical trials in 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 specialist in pediatric and adolescent HIV infection. If that 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 generally requires a multidisciplinary team approach that includes physicians, nurses, nutritionists, pharmacists, dentists, psychologists, social workers, child life specialists, and outreach workers.
- Health care providers contemplating use of ARV drugs to treat infants, children, or adolescents should consider certain factors that influence adherence to therapy, including:
    - availability and palatability of drug formulations;
    - impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food;
    - ability of the children's caregiver or the adolescents themselves 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 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 of growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition is essential in the care of HIV-infected children because those factors may significantly influence quality of life.

‡ In areas where enrollment in clinical trials is possible, enrollment of children in available trials should be discussed with the children's caregivers. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDS*info* website (http://aidsinfo.nih.gov/ClinicalTrials/) or by telephone at 1-800-448-0440.

References

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