Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

August 16, 2010

Developed by the Panel on Antiretroviral Therapy
and Medical Management of HIV-Infected Children

François-Xavier Bagnoud Center, UMDNJ
The Health Resources and Services Administration
The National Institutes of Health

How to Cite the Pediatric Guidelines:
Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 16, 2010; pp 1-219. Available at **http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf**. Accessed (insert date) [include page numbers, table number, etc. if applicable]

Use of antiretrovirals in pediatric patients is evolving rapidly.
These guidelines are updated regularly to provide current information.
The most recent information is available at **http://aidsinfo.nih.gov**.

What's New in the Pediatric Guidelines?

The updated *Guidelines for the Use of Antiretroviral Agents in Pediatric Infection* include the following changes made to the February 23, 2009, version of the guidelines. Key updates are also highlighted throughout the guidelines.

Ratings for Primary Recommendations

The key change prominent in the current guidelines is development of a ratings system to indicate strength and quality of evidence for each major recommendation. The strength of each recommendation is indicated by a letter (A = Strong, B = Moderate, C = Optional); the quality of the evidence supporting each recommendation is represented by a Roman numeral (I, II, III). In addition, because many pediatric recommendations will be based on data from clinical trials or observational studies in adults, with only safety and pharmacokinetic data in children, evidence ratings that are based on adult data will be indicated with an asterisk (*).

Format Changes/New Sections

Previous Appendix B: Characteristics of Available Antiretroviral Drugs and Supplement I: Pediatric Antiretroviral Drug Information

- Information in the previous Appendix B: Characteristics of Available Antiretroviral Drugs and pevious Supplement I: Pediatric Antiretroviral Drug Information of the February 23, 2009, guidelines has been combined into a new format with a table for each drug summarizing drug formulation, dosing recommendations, important adverse effects, and special instructions. Each table is followed by a short text section that includes important pediatric experience and references for that particular drug. Updated information on drugs is provided.

Previous Supplement III: Adverse Drug Effects

- This supplement to the previous version of the guidelines describes specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The supplement has been modified into a table format and included in the body of the current guidelines, with information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provides selected references regarding these toxicities in pediatric patients.

Previous Supplement II: Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy

- This supplement on pain management and nutrition included in the previous version of the guidelines has been retired. (See *Supplement II: Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy* in the archived February 23, 2009, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* at **http://www.aidsinfo.nih.gov**.)

Key Updates

Updates to the various sections of the guidelines include the following new information/key changes:

Diagnosis of HIV Infection in Infants

- Viral diagnostic testing at birth is recommended for infants at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal antiretroviral therapy or who had HIV viral loads $\geq$1,000 copies/mL close to time of delivery (BIII). Viral diagnostic testing continues to be recommended for all HIV-exposed infants at age 14–21 days, 1–2 months, and 4–6 months (AII).

- An HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant virologic diagnostic testing (AII).

When to Start

- Antiretroviral therapy continues to be recommended for all children younger than 12 months of age regardless of clinical, immunologic, or virologic symptoms (AI).
- However, whereas prior guidelines said antiretroviral therapy could be *considered* for asymptomatic or mildly symptomatic children with CD4 ≥25% (or ≥350 cells/uL if age ≥5 years) and HIV RNA ≥100,000 copies/mL, the current guidelines now *recommend* therapy in this situation (BII). Additionally, whereas prior guidelines recommended *deferral* of therapy for asymptomatic or mildly symptomatic children with CD4 ≥25% (or ≥350 cells/uL if age ≥5 years) and HIV RNA <100,000 copies/mL, the current guidelines say therapy can be *considered or deferred* (CIII). Specific recommendations are:
    - Initiation of antiretroviral therapy is *recommended* for children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level (AI*).
    - Initiation of antiretroviral therapy is also *recommended* for children age ≥1 year who have met the age-related CD4 threshold for initiating treatment (CD4 <25% for children 1 to <5 years of age (AII) and <350 cells/mm^3 for children ≥5 years of age (AI*), regardless of symptoms or plasma HIV RNA level).
    - Initiation of antiretroviral therapy is also *recommended* for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or the following Clinical Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) *and* have CD4 ≥25% for children 1 to <5 years of age or ≥350 cells/mm^3 for children ≥5 years of age *and* have plasma HIV RNA ≥100,000 copies/mL (BII).
    - Initiation of antiretroviral therapy may be *considered or deferred* for children age ≥1 year who are asymptomatic or have mild symptoms and who have CD4 ≥25% for children 1 to <5 years of age and ≥350 cell/mm^3 for children ≥5 years of age *and* have plasma HIV RNA <100,000 copies/mL (CIII).

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children

- Recent data from clinical trials of nevirapine versus lopinavir/ritonavir-based therapy in children with single-dose nevirapine exposure for prevention of mother-to-child transmission of HIV are discussed.
- NNRTI-based therapy is not recommended for infants or children age <3 years with single-dose nevirapine exposure (AI).
- Darunavir in combination with low-dose ritonavir is now recommended as an alternative protease inhibitor for initial therapy in children age ≥6 years (AI*).
- Nelfinavir has been moved from an alternative protease inhibitor for initial therapy to a protease inhibitor for use in special circumstances in children age ≥2 years (AII).

Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents

- Results of several new studies regarding interventions to improve adherence in children and/or adolescents are described.

Additional Updates

- References have been updated in many sections.

Table of Contents

Members of Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children

These updated *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the François-Xavier Bagnoud Center (FXBC), University of Medicine and Dentistry of New Jersey (UMDNJ); the Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

Panel Co-Chairs:

Peter Havens, MS, MD	Medical College of Wisconsin, Milwaukee, WI
Russell Van Dyke, MD	Tulane University School of Medicine, New Orleans, LA
Geoffrey A. Weinberg, MD	University of Rochester School of Medicine and Dentistry, Rochester, NY

Panel Executive Secretary:

Lynne Mofenson, MD	National Institutes of Health, Rockville, MD

Members of the Panel:

Elaine J. Abrams, MD	Columbia University, New York, NY
Edmund Capparelli, MD	University of California – San Diego, La Jolla, CA
Diana Clarke, PharmD	Boston Medical Center, Boston, MA
Patricia M. Flynn, MD	St. Jude's Medical Center, Memphis, TN
Marc D. Foca, MD, MPH	Columbia University College of Physicians and Surgeons, New York, NY
Nancy Hutton, MD	Johns Hopkins School of Medicine, Baltimore, MD
Ebony Johnson, MHS	Children's National Medical Center, Washington DC
Paul A. Krogstad, MD	University of California – Los Angeles, Los Angeles, CA
James McAuley, MD, MPH	Rush University Medical Center, Chicago, IL
Mark Mirochnick, MD	Boston Medical Center, Boston, MA
Paul Palumbo, MD	Dartmouth Medical School, Dartmouth, NH
Mary E. Paul, MD	Baylor College of Medicine, Houston, TX
Vicki B. Peters, MD	New York City Department of Health and Mental Hygiene, New York, NY
Richard M. Rutstein, MD	Children's Hospital of Philadelphia, Philadelphia, PA
Dorothy Shaw, BA	Birmingham, AL
Andrew Wiznia, MD	Jacob Medical Center, Bronx, NY

Members from the Department of Health and Human Services:

Kenneth L. Dominguez, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Brian Feit, MPA	Health Resources and Services Administration, Rockville, MD
Edward Handelsman, MD	National Institutes of Health, Bethesda, MD
Rohan Hazra, MD	National Institutes of Health, Bethesda, MD
Patrick Jean-Philippe, MD	National Institutes of Health, Bethesda, MD
Linda Lewis, MD	Food and Drug Administration, Rockville, MD
George Siberry, MD, MPH	National Institutes of Health, Bethesda, MD

Nonvoting Observers from the François-Xavier Bagnoud Center:

Carolyn Burr, RN, EdD	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Supriya Modey, MPH, MBBS	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Andrea Norberg, MS, RN	AETC National Resource Center at the François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Deborah Storm, PhD	François-Xavier Bagnoud Center School of Nursing, UMDNJ, Newark, NJ

Introduction (Updated August 16, 2010)

These guidelines address issues specific to the use of antiretroviral therapy for HIV-infected infants, children, and prepubertal adolescents. Included is information on the management of adverse events of antiretroviral drugs in children and details on pediatric data related to antiretroviral 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* Web site at **http://aidsinfo.nih.gov**.

Separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children *[1]* and for the use of antiretroviral agents in HIV-infected postpubertal adolescents and adults *[2]* are also available on the AIDS*info* Web site. Because these guidelines were developed for the United States, they 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.**

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 antiretroviral combination therapies in children. HIV mortality has decreased by more than 80%–90% since the introduction of protease inhibitor-containing combinations, and opportunistic and other related infections have significantly decreased in the era of highly active antiretroviral therapy (HAART) *[3-8]*. Advances including resistance testing and the ability to measure antiretroviral 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 antiretroviral 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 that improve adherence with less frequent dosing schedules. Improved monitoring and dosing schedules have also led to a decrease in drug failure due to toxicity. The use of antiretroviral therapy 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 decline *[9]*. Finally, children living with HIV infection are, as a group, growing older, bringing new challenges of adherence, drug resistance, and management of multiple drugs.

Although the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected people, there are unique considerations for HIV-infected infants, children, and adolescents, including:

- Acquisition of infection through perinatal exposure for many infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to zidovudine and other antiretroviral 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 parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
- 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 antiretroviral treatment for infants, children, and adolescents.

These recommendations represent the current state of knowledge regarding the use of antiretroviral 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 process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

Page 1 of 2

Topic	Comment
Goal of the Guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral 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 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). 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 on **page viii** of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in **Appendix A** of this document.
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 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	As 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 a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.

Topic	Comment
Other guidelines	These guidelines focus on HIV-infected infants, children, and adolescents through puberty. Separate guidelines outline the use of antiretroviral therapy in pregnant HIV-infected women and interventions for prevention of mother-to-child transmission, antiretroviral therapy for nonpregnant HIV-infected adults and postpubertal adolescents, and antiretroviral prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). These guidelines focus on HIV-infected children from infancy through puberty. For more detailed discussion on issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents.
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. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* 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@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 relies on efficacy data from adult trials in addition to safety and pharmacokinetic data in children, recommendations for antiretroviral 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) there are supplemental data on pharmacokinetics of the drug in children so that systemic exposure in adults and children are similar; and
(3) studies supporting the safety of the drug in pediatric patients are provided *[10]*.

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 from adult studies (especially randomized clinical trials) than from pediatric studies related to use of antiretroviral drugs. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

- **Quality of Evidence 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 antiretroviral-naïve patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and pharmacokinetic 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 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
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 with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

†Studies that include children or children/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 *[11-13]*. 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 antiretroviral drugs produced.
- Although some information regarding the efficacy of antiretroviral 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 antiretroviral drug in children.

* 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 AIDS*info* Web site (**http://aidsinfo.nih.gov/ClinicalTrials/**) or by telephone at 1-800-448-0440.

- 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 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, and outreach workers.
- Health care providers considering antiretroviral treatment 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 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 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 antiretroviral regimen should include consideration of factors that may limit future treatment options, such as the presence of or potential for the development of antiretroviral resistance. 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.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
3. Gortmaker S, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med.* 2001;345(21):1522-1528.
4. Gona P, van Dyke R, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA.* 2006;296(3):292-300.
5. Selik RM, Lindegren ML. Changes in deaths reported with human immunodeficiency virus infection among United States children less than thirteen years old, 1987 through 1999. *Pediatr Infect Dis J.* 2003;22(7):635-641.
6. Gibb DM, Duong T, Tookey PA, et al. National Study of HIV in Pregnancy and Childhood Collaborative HIV Paediatric Study. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ.* 2003;327(7422):1019.
7. McConnell MS, Byers RH, Frederick T, et al. Trends in antiretroviral therapy use and survival rates for a large cohort of HIV-infected children and adolescents in the United States, 1989-2001. *J Acquir Immune Defic Syndr.* 2005;38(4):488-494.
8. Judd A, Doerholt K, Tookey PA, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clin Infect Dis.* 2007;45(7):918-924.
9. Centers for Disease Control and Prevention. Reduction in perinatal transmission of HIV infection - United States, 1985-2005. *MMWR.* 2006;55(21):592-597.
10. Food and Drug Administration. Guidance for Industry: General considerations for pediatric pharmacokinetic studies for drugs and biological products. November 30, 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf
11. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral and revised recommendations for HIV screening of pregnant women. *MMWR.* 2001;50(RR-19):1-110.

12. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. *Pediatrics.* 2000;106(6):E88.
13. American College of Obstetricians and Gynecologists. Human immunodeficiency virus infections in pregnancy. *Int J Gynaecol Obstet.* 1997;57(1):73-80.

Identification of Perinatal HIV Exposure

(Updated August 16, 2010)

Panel's Recommendations:

- ***Universal counseling and voluntary HIV testing early in pregnancy, including opt-out testing, are recommended as standard of care for all pregnant women in the United States (AII).***
- ***Repeat HIV testing is recommended in the third trimester for women who have negative HIV antibody tests earlier in pregnancy if they are at high risk of HIV infection because of behavior or residence in a high-prevalence area (AII).***
- ***Women seen at labor with undocumented HIV status should undergo rapid HIV antibody testing, and women with a positive antibody test should initiate intrapartum antiretroviral prophylaxis (AII).***
- ***If acute HIV infection is suspected in a pregnant woman, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection (AII).***
- ***Women who have not been tested for HIV prior to or during labor should be offered rapid HIV antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing; if the mother or infant is HIV antibody positive, infant antiretroviral prophylaxis should be initiated as soon as possible and the mother advised not to breastfeed pending results of confirmatory HIV antibody testing (AII).***

Appropriate treatment of HIV-infected infants requires HIV-exposed infants to be identified as soon as possible, which can be best accomplished through the identification of HIV-infected women before or during pregnancy. Universal HIV counseling and voluntary HIV testing, including consent using an opt-out approach, are recommended as the standard of care for all pregnant women in the United States by the Panel, the U.S. Public Health Service (USPHS), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force *[1-6]*. An opt-out approach notifies a pregnant woman that HIV testing will be performed as part of routine care unless she chooses not to be tested for HIV *[7]*.

Early identification of HIV-infected women is crucial for their health and for the care of HIV-exposed and HIV-infected children. Knowledge of antenatal maternal HIV infection enables:

- HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infections for their own health;
- Provision of antiretroviral chemoprophylaxis during pregnancy, during labor, and to the newborn to reduce the risk of HIV transmission from mother to child *[8]*;
- Counseling of HIV-infected women about the indications for and potential benefits of scheduled cesarean section delivery to reduce perinatal HIV transmission *[8-11]*;
- Counseling of HIV-infected women about the risks of HIV transmission through breast milk and advising against breastfeeding in the United States and other countries where safe alternatives to breast milk are available *[12]*;
- Initiation of prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) in all HIV-exposed infants with indeterminate HIV infection status or who have documented HIV infection beginning at age 4 to 6 weeks *[13]*; and
- Early diagnostic evaluation of HIV-exposed infants to permit early initiation of antiretroviral therapy in infected infants *[2, 14]*.

REPEAT HIV TESTING IN THE THIRD TRIMESTER

Repeat HIV testing is recommended in the third trimester, preferably <36 weeks gestation, for women with initially negative HIV antibody tests who are at high risk of HIV infection and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet 1 or more of the following criteria: women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women 15–45 years of age; women who receive health care in facilities in which prenatal screening identifies at least 1 HIV-infected pregnant woman per 1,000 women screened; women who are known to be at high risk of acquiring HIV (e.g., injection drug users or partners of injection drug users, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than 1 sex partner during this pregnancy or diagnosis of a new sexually transmitted infection during pregnancy); and women who have signs or symptoms of acute HIV infection *[3-4, 15]*. Women who have declined testing earlier in pregnancy should have testing offered again during the third trimester. There is evidence that the risk of HIV acquisition may be significantly higher during pregnancy than in the postpartum period *[16]*. If acute HIV infection is suspected, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection.

RAPID HIV TESTING DURING LABOR IN WOMEN WITH UNKNOWN HIV STATUS

Use of rapid test kits or an expedited enzyme-linked immunosorbant assay (ELISA) to detect HIV antibody is recommended to screen women who are seen at labor and have undocumented HIV status in order to identify HIV exposure in their infants *[2-4, 14]*. Any hospital offering intrapartum care should have rapid HIV testing available and should have in place policies and procedures to assure that staff are prepared to provide patient education about rapid HIV testing, that appropriate antiretroviral medications are available whenever needed, and that follow-up procedures for women found to be HIV infected and their infants are in place. Rapid tests have been found to be feasible, accurate, timely, and useful both in providing prompt access to intrapartum and neonatal antiretroviral prophylaxis and in reducing perinatal HIV transmission *[17]*. Results of rapid tests can be obtained within minutes to a few hours and are as accurate as standard ELISA antibody testing *[18-19]*. A positive rapid HIV test result must be followed by a confirmatory test such as a Western blot (or immunofluorescent antibody [IFA]); a standard ELISA should not be used as a confirmatory test for a rapid HIV antibody test *[19]*. A negative single rapid test does not need confirmation. The immediate initiation of antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV is strongly recommended while awaiting confirmatory testing results after an initial positive rapid HIV test *[2, 6, 8, 14]*.

HIV COUNSELING AND TESTING DURING POSTNATAL PERIOD

Women who have not been tested for HIV prior to or during labor should be offered rapid testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing, with counseling and consent of the mother unless state law allows testing without consent *[3, 8, 20-21]*. Because neonatal antiretroviral chemoprophylaxis should be initiated as soon as possible after birth to be effective in preventing mother-to-child transmission, use of rapid HIV antibody assays or expedited ELISA testing to allow prompt identification of HIV-exposed infants is critical. It is strongly recommended that infant antiretroviral prophylaxis be initiated while awaiting confirmatory testing results after an initial positive rapid test in the mother or the infant, and women with positive rapid HIV test results should be advised not to initiate breastfeeding pending results of confirmatory testing. If the confirmatory test is negative, the infant antiretroviral prophylaxis can be discontinued and the mother can initiate breastfeeding. Mechanisms should be developed to facilitate rapid HIV screening for infants who have been abandoned and are in the custody of the state.

References

1. American Academy of Pediatrics Committee of Pediatric AIDS and American College of Obstetrics and Gynecology. Human immunodeficiency virus screening. Joint statement of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. *Pediatrics.* 1999;104(1 Pt 1):128.
2. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics.* 2008;122(5):1127-1134.
3. American College of Obstetricians and Gynecologists. ACOG committee opinion number 304, November 2004. Prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. *Obstet Gynecol.* 2004;104(5 Pt 1):1119-1124.
4. CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care-settings. *MMWR.* 2006;55(No. RR-14).
5. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. *Pediatrics.* 2000;106(6):E88.
6. U.S. Preventive Task Force. Screening for HIV: recommendation statement. *Ann Intern Med.* 2005;143(1):32-37.
7. Centers for Disease Control and Prevention (CDC). HIV testing among pregnant women--United States and Canada, 1998-2001. *MMWR Morb Mortal Wkly Rep.* 2002;51(45):1013-1016.
8. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
9. American College of Obstetricians and Gynecologists. ACOG committee opinion scheduled Cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234, May 2000 (replaces number 219, August 1999). *Int J Gynaecol Obstet.* 2001;73(3):279-281.
10. Jamieson DJ, Read JS, Kourtis AP, et al. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S96-100.
11. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis.* 2010;50(4):585-596.
12. Read JS. Human milk, breastfeeding, and transmission of human immunodeficiency virus type 1 in the United States. American Academy of Pediatrics Committee on Pediatric AIDS. *Pediatrics.* 2003;112(5):1196-1205.
13. Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
14. Havens PL, Mofenson LM. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175-187.
15. Sansom SL, Jamieson DJ, Farnham PG, et al. Human immunodeficiency virus retesting during pregnancy: costs and effectiveness in preventing perinatal transmission. *Obstet Gynecol.* 2003;102(4):782-790.
16. Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet.* 2005;366(9492):1182-1188.
17. Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Rapid HIV-1 testing during labor: a multicenter study. *JAMA.* 2004;292(2):219-223.
18. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: A practical guide and model protocol 2004.
19. Centers for Disease Control and Prevention (CDC). Protocols for confirmation of reactive rapid hiv tests. *MMWR.* 2004;53(10):221-222.
20. New York State Department of Public Health. HIV testing and diagnosis in infants and children. 2005; http://www.hivguidelines.org/wp-content/uploads/2009/05/p-test.pdf.
21. New York State Register. Title 10 NYCRR, Subpart 69-1.3, revision effective 08/01/99. 1998;20(51):8-11.

Diagnosis of HIV Infection in Infants

(Updated August 16, 2010)

Panel's Recommendations:

- ***Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months, because maternal HIV antibody may persist in this age group and give a false-positive antibody test in an uninfected child (AII).***
- ***Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at age 14–21 days; 1–2 months; and 4–6 months (AII).***
- ***Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection (BIII).***
- ***HIV DNA PCR and HIV RNA assays are recommended as preferred virologic assays (AII).***
- ***Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples (AI).***
- ***Definitive exclusion of HIV infection should be based on at least two negative virologic tests (one at ≥1 month and one at ≥4 months of age) (AII).***
- ***Some experts confirm the absence of HIV infection at 12–18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of HIV antibody (BIII).***
- ***In children age ≥18 months, HIV antibody assays alone can be used for diagnosis (AII).***

CHOICE OF DIAGNOSTIC TEST

HIV infection can be definitively diagnosed through the use of virologic assays in most nonbreastfed HIV-infected infants by 1 month of age and in virtually all infected infants by 4 months of age. Tests for antibodies to HIV, including newer rapid tests, do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies; therefore a virologic test should be used *[1]*. A positive virologic test (i.e., detection of HIV by DNA polymerase chain reaction [PCR] or RNA assays) indicates likely HIV infection and should be confirmed by a repeat virologic test on a second specimen as soon as possible after the first test result becomes available. HIV culture is not used for routine HIV diagnostic testing. The use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in the first months of life are less than that of other HIV virologic tests *[2-3]*.

HIV DNA PCR

HIV DNA PCR is a sensitive technique used to detect specific HIV viral DNA in a patient's peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at <48 hours of age is less than 40% but increases to more than 90% by 2–4 weeks of age *[4-8]*.

In a meta-analysis, 38% (90% confidence interval [CI] = 29%–46%) of infected children had positive HIV DNA PCR tests by 48 hours of age *[9]*. No substantial change in sensitivity during the first week of life was observed, but sensitivity increased rapidly during the second week, with 93% of infected children (90% CI = 76%–97%) testing positive by HIV DNA PCR by age 14 days. By age 28 days, HIV DNA PCR had 96% sensitivity and 99% specificity to identify HIV proviral DNA in PBMCs.

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in the plasma and are as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. Studies have demonstrated sensitivities of 25%–40% during the first weeks of life, increasing to 90%–100% by 2–3 months of age *[7-8, 10-16]*. Similarly, specificity is comparable between the two tests, although the detection of low levels of HIV RNA

(<5,000 copies/mL) may not be reproducible and tests with low levels of HIV RNA should be repeated before they are interpreted as documenting the presence of HIV infection in an infant. An HIV RNA assay can be used as the confirmatory test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (see HIV subtype section below). However, although HIV DNA PCR remains positive even in individuals receiving highly active antiretroviral therapy *[17]*, it is unknown whether the sensitivity of RNA assays might be affected by maternal antenatal treatment with combination antiretroviral drugs and/or infant antiretroviral prophylaxis.

HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing *[18-21]*.

HIV Culture

HIV culture is not used for routine HIV diagnostic testing. It is generally not available outside of research laboratories. Although HIV culture has a sensitivity similar to that of HIV DNA PCR *[22]*, it is more complex and expensive to perform than DNA PCR or RNA assays and may require 2–4 weeks for definitive results.

ISSUES RELATED TO DIAGNOSIS OF NON-SUBTYPE B HIV INFECTION

Although HIV subtype B is the predominant viral subtype found in the United States, non-subtype B viruses predominate in some other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia *[23-25]*. Currently available HIV DNA PCR tests are less sensitive in the detection of non-subtype B HIV, and false-negative HIV DNA PCR assays have been reported in infants infected with non-subtype B HIV *[26-29]*. In an evaluation of perinatally infected infants diagnosed in New York State in 2001–2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants diagnosed between 1998 and 1999 *[30]*.

Some of the currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection *[31-34]*, although even these assays may not detect or properly quantify some non-B subtypes, particularly the more uncommon group O HIV subtypes *[33, 35-36]*. When non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR, repeat testing using one of the newer RNA assays shown to be more sensitive in the detection of non-subtype B HIV is recommended (e.g., Amplicor HIV-1 Monitor 1.5 [Roche Molecular Systems, Pleasanton, CA], NucliSens HIV-1 QT [bioMerieux, Inc., Durham, NC], Versant Quantiplex HIV RNA 3.0 [bDNA] [Bayer Corporation, Tarrytown, NY]; AmpliPrep/TaqMan HIV-1 Test [Roche Diagnostics, Indianapolis, IN]; Real Time HIV-1 Assay [Abbott Molecular Incorporated, Des Plaines, IL] and the APTIMA HIV-1 RNA Qualitative Assay [Gen-Probe Incorporated San Diego, CA]).

When evaluating an infant whose mother and/or father comes from an area endemic for non-subtype B HIV, such as Africa and Southeast Asia, clinicians should consider conducting initial testing using one of the assays more sensitive for non-subtype B virus (for example, one of the newer RNA assays mentioned above) *[33, 37]*. In a child with negative HIV DNA PCR and RNA assays but in whom non-subtype B infection is suspected, the clinician should consult with an expert in pediatric HIV infection and the child should undergo close clinical monitoring and definitive HIV serologic testing at age 18 months.

TIMING OF DIAGNOSTIC TESTING IN INFANTS WITH KNOWN PERINATAL HIV EXPOSURE

Virologic diagnostic testing of the HIV-exposed infant should be performed at age 14–21 days, at age 1–2 months, and at age 4–6 months. Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection.

HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples, regardless of child's age. A positive HIV antibody test with confirmatory Western blot (or IFA) at age ≥18 months confirms HIV infection with the exception of rare late seroreverters (see HIV antibody section below) *[1]*.

HIV infection can be *presumptively* excluded in nonbreastfed infants with two or more negative virologic tests, with one test obtained at ≥14 days of age and one obtained at ≥1 month of age; or one negative virologic test result obtained at ≥2 months of age; or one negative HIV antibody test result obtained at ≥6 months of age *[1, 38]*. *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at 4–6 weeks of age until they are determined to be HIV uninfected or *presumptively* uninfected with HIV *[39]*. Thus, initiation of PCP prophylaxis can be avoided or, if prophylaxis was initiated, can be stopped, if the infant has negative virologic tests at 2 weeks of age and at 1 month of age, or if virologic testing is negative at or beyond 2 months of age. *Definitive* exclusion of HIV infection in a nonbreastfed infant is based on two or more negative virologic tests, with one obtained at ≥1 month of age and one at ≥4 months of age, or two negative HIV antibody tests from separate specimens obtained at ≥6 months of age. For both *presumptive* and *definitive* exclusion of HIV infection, the child must have no other laboratory (e.g., no positive virologic test results or low CD4 count/percent) or clinical evidence of HIV infection. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at 12–18 months of age to document seroreversion to HIV antibody negative status.

Virologic Testing at Birth (Optional)

Virologic testing at birth may be considered for newborns at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care, prenatal antiretroviral therapy, or who had HIV viral loads ≥1,000 copies/mL close to time of delivery. As many as 30%–40% of HIV-infected infants can be identified by 48 hours of age *[4, 9]*. Blood samples from the umbilical cord should not be used for diagnostic evaluations due to the potential contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection during the intrauterine period from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection *[40]*. Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and therefore should receive more aggressive therapy *[40-41]*. However, data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels were present between infants with a positive HIV culture within 48 hours of birth and those with a first positive culture after 7 days of age, these differences were no longer statistically significant after 2 months of age *[42]*. HIV RNA levels after the first month of life were more predictive of rapid disease progression than the time at which HIV culture tests were positive *[42]*.

Virologic Testing at Age 14–21 Days

The diagnostic sensitivity of virologic assays increases rapidly by age 2 weeks *[9]*, and early identification of infection would permit discontinuation of neonatal antiretroviral prophylaxis and further evaluation for initiation of combination antiretroviral therapy (see **When to Initiate Therapy in Antiretroviral-Naïve HIV-Infected Infants Younger than 12 Months** and **Table 7**).

Virologic Testing at Age 1–2 Months

Infants with negative virologic tests before 1 month of age should be retested at 1–2 months of age. Most HIV-exposed neonates will receive 6 weeks of neonatal antiretroviral prophylaxis. Although antiretroviral agents could theoretically affect the predictive value of HIV virologic testing in neonates, the use of antepartum/intrapartum/neonatal zidovudine single-drug prophylaxis did not delay the detection of HIV by culture in infants in PACTG protocol 076 and has not decreased the sensitivity and predictive values of many virologic assays *[10, 12-13, 16, 38, 43-44]*. The affect of prenatal and neonatal combination antiretroviral regimens on the sensitivity of virologic tests for HIV-exposed infants needs to be examined. An infant with two negative virologic tests, one at ≥14 days and one at ≥1 month of age can be viewed as *presumptively* uninfected and would not need to initiate PCP prophylaxis, assuming the child has no laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection.

Virologic Testing at Age 4–6 Months

HIV-exposed children who have had repeatedly negative virologic assays at 14–21 days of age and at 1–2 months of age should be retested at 4–6 months of age for *definitive* exclusion of HIV infection.

Antibody Testing at Age 6 Months or Older

Two or more negative HIV antibody tests performed at ≥6 months of age can also be used to *definitively* exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory evidence of HIV infection.

Antibody Testing at Age 12–18 Months to Document Seroreversion

Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing serology repeated between ages 12–18 months to confirm that maternal HIV antibodies transferred to the infant *in utero* have disappeared, if there has not been previous confirmation of two negative antibody tests. Although the proportion of infants who serorevert between 15 and 18 months of age is close to 100%, as many as 95% of infants may serorevert by 12 months of age; factors that might influence the time to seroreversion include the staging of maternal disease or the sensitivity of the assay *[1, 45-48]*.

Antibody Testing at Age 18 Months or Older

HIV infection can be diagnosed in children 18 months of age or older with a positive HIV antibody test and a confirmatory Western blot (or IFA). On rare occasions, nonbreastfed HIV-exposed infants with no other route of HIV transmission (e.g., sexual abuse or receipt of solid food premasticated by an HIV-1–infected caregiver) and no prior clinical or virologic laboratory evidence of HIV infection may have residual antibody at 18 months of age. These infants should have monthly repeat antibody testing because they may be late seroreverters, as late as 24 months *[48]*.

References

1. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
2. Guay LA, Hom DL, Kabengera SR, et al. HIV-1 ICD p24 antigen detection in ugandan infants: use in early diagnosis of infection and as a marker of disease progression. *J Med Virol.* 2000;62(4):426-434.
3. New York State Department of Public Health. HIV testing and diagnosis in infants and children. 2005; http://www.hivguidelines.org/wp-content/uploads/2009/05/p-test.pdf.
4. Bremer JW, Lew JF, Cooper E, et al. Diagnosis of infection with human immunodeficiency virus type 1 by a DNA polymerase chain reaction assay among infants enrolled in the Women and Infants' Transmission Study. *J Pediatr.* 1996;129(2):198-207.

5. Charbonneau TT, Wade NA, Weiner L, et al. Vertical transmission of HIV in New York State: a basis for statewide testing of newborns. *AIDS Patient Care STDS.* 1997;11(4):227-236.
6. Pugatch D. Testing infants for human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(7):711-712.
7. Havens PL, Mofenson LM. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175-187.
8. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics.* 2008;122(5):1127-1134.
9. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS.* 1995;9(9):F7-11.
10. Cunningham CK, Charbonneau TT, Song K, et al. Comparison of human immunodeficiency virus 1 DNA polymerase chain reaction and qualitative and quantitative RNA polymerase chain reaction in human immunodeficiency virus 1-exposed infants. *Pediatr Infect Dis J.* 1999;18(1):30-35.
11. Delamare C, Burgard M, Mayaux MJ, et al. HIV-1 RNA detection in plasma for the diagnosis of infection in neonates. The French Pediatric HIV Infection Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;15(2):121-125.
12. Lambert JS, Harris DR, Stiehm ER, et al. Performance characteristics of HIV-1 culture and HIV-1 DNA and RNA amplification assays for early diagnosis of perinatal HIV-1 infection. *J Acquir Immune Defic Syndr.* 2003;34(5):512-519.
13. Nesheim S, Palumbo P, Sullivan K, et al. Quantitative RNA testing for diagnosis of HIV-infected infants. *J Acquir Immune Defic Syndr.* 2003;32(2):192-195.
14. Simonds RJ, Brown TM, Thea DM, et al. Sensitivity and specificity of a qualitative RNA detection assay to diagnose HIV infection in young infants. Perinatal AIDS Collaborative Transmission Study. *AIDS.* 1998;12(12):1545-1549.
15. Steketee RW, Abrams EJ, Thea DM, et al. Early detection of perinatal human immunodeficiency virus (HIV) type 1 infection using HIV RNA amplification and detection. New York City Perinatal HIV Transmission Collaborative Study. *J Infect Dis.* 1997;175(3):707-711.
16. Young NL, Shaffer N, Chaowanachan T, et al. Early diagnosis of HIV-1-infected infants in Thailand using RNA and DNA PCR assays sensitive to non-B subtypes. *J Acquir Immune Defic Syndr.* 2000;24(5):401-407.
17. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.
18. Kerr RJ, Player G, Fiscus SA, et al. Qualitative human immunodeficiency virus RNA analysis of dried blood spots for diagnosis of infections in infants. *J Clin Microbiol.* 2009;47(1):220-222.
19. U.S. Food and Drug Administration. APTIMA HIV-1 RNA Qualitative Assay. 2009; http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm149922.htm.
20. Stevens WS, Noble L, Berrie L, et al. Ultra-high-throughput, automated nucleic acid detection of human immunodeficiency virus (HIV) for infant infection diagnosis using the Gen-Probe Aptima HIV-1 screening assay. *J Clin Microbiol.* 2009;47(8):2465-2469.
21. Walter J, Kuhn L, Semrau K, et al. Detection of low levels of human immunodeficiency virus (HIV) may be critical for early diagnosis of pediatric HIV infection by use of dried blood spots. *J Clin Microbiol.* 2009;47(9):2989-2991.
22. McIntosh K, Pitt J, Brambilla D, et al. Blood culture in the first 6 months of life for the diagnosis of vertically transmitted human immunodeficiency virus infection. The Women and Infants Transmission Study Group. *J Infect Dis.* 1994;170(4):996-1000.
23. Osmanov S, Pattou C, Walker N, et al. Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. *J Acquir Immune Defic Syndr.* 2002;29(2):184-190.
24. Auwanit W, Isarangkura-Na-Ayuthaya P, Kasornpikul D, et al. Detection of drug resistance-associated and background mutations in human immunodeficiency virus type 1 CRF01_AE protease and reverse transcriptase derived from drug treatment-naive patients residing in central Thailand. *AIDS Res Hum Retroviruses.* 2009;25(6):625-631.
25. Deshpande A, Jauvin V, Pinson P, et al. Phylogenetic analysis of HIV-1 reverse transcriptase sequences from 382 patients recruited in JJ Hospital of Mumbai, India, between 2002 and 2008. *AIDS Res Hum Retroviruses.* 2009;25(6):633-635.

26. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infect Dis.* 1996;174(1):244-245.
27. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J.* 2002;21(9):885-886.
28. Obaro SK, Losikoff P, Harwell J, et al. Failure of serial human immunodeficiency virus type 1 DNA polymerase chain reactions to identify human immunodeficiency virus type 1 clade A/G. *Pediatr Infect Dis J.* 2005;24(2):183-184.
29. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis.* 2002;34(3):417-418.
30. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
31. Antunes R, Figueiredo S, Bartolo I, et al. Evaluation of the clinical sensitivities of three viral load assays with plasma samples from a pediatric population predominantly infected with human immunodeficiency virus type 1 subtype G and BG recombinant forms. *J Clin Microbiol.* 2003;41(7):3361-3367.
32. Plantier JC, Gueudin M, Damond F, et al. Plasma RNA quantification and HIV-1 divergent strains. *J Acquir Immune Defic Syndr.* 2003;33(1):1-7.
33. Swanson P, de Mendoza C, Joshi Y, et al. Impact of human immunodeficiency virus type 1 (HIV-1) genetic diversity on performance of four commercial viral load assays: LCx HIV RNA Quantitative, AMPLICOR HIV-1 MONITOR v1.5, VERSANT HIV-1 RNA 3.0, and NucliSens HIV-1 QT. *J Clin Microbiol.* 2005;43(8):3860-3868.
34. Triques K, Coste J, Perret JL, et al. Efficiencies of four versions of the AMPLICOR HIV-1 MONITOR test for quantification of different subtypes of human immunodeficiency virus type 1. *J Clin Microbiol.* 1999;37(1):110-116.
35. Geelen S, Lange J, Borleffs J, et al. Failure to detect a non-B HIV-1 subtype by the HIV-1 Amplicor Monitor test, version 1.5: a case of unexpected vertical transmission. *AIDS.* 2003;17(5):781-782.
36. Krogstad P, Eshleman SH, Geng Y, et al. Mother-to-child transmission in the United States of subtypes D and A/G human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses.* 2002;18(6):413-417.
37. Rouet F, Montcho C, Rouzioux C, et al. Early diagnosis of paediatric HIV-1 infection among African breast-fed children using a quantitative plasma HIV RNA assay. *AIDS.* 2001;15(14):1849-1856.
38. Read JS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics.* 2007;120(6):e1547-1562.
39. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep.* 2009;58(RR-11):1-166.
40. Bryson YJ, Luzuriaga K, Sullivan JL, et al. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *N Engl J Med.* 1992;327(17):1246-1247.
41. Mayaux MJ, Burgard M, Teglas JP, et al. Neonatal characteristics in rapidly progressive perinatally acquired HIV-1 disease. The French Pediatric HIV Infection Study Group. *JAMA.* 1996;275(8):606-610.
42. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med.* 1997;336(19):1337-1342.
43. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994;331(18):1173-1180.
44. Kovacs A, Xu J, Rasheed S, et al. Comparison of a rapid nonisotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human immunodeficiency virus type 1 infection in neonates and children. *Pediatr Infect Dis J.* 1995;14(11):948-954.
45. Alcantara KC, Pereira GA, Albuquerque M, et al. Seroreversion in children born to HIV-positive and AIDS mothers from Central West Brazil. *Trans R Soc Trop Med Hyg.* 2009;103(6):620-626.
46. Gulia J, Kumwenda N, Li Q, et al. HIV seroreversion time in HIV-1-uninfected children born to HIV-1-infected mothers in Malawi. *J Acquir Immune Defic Syndr.* 2007;46(3):332-337.
47. Moodley D, Bobat RA, Coutsoudis A, et al. Predicting perinatal human immunodeficiency virus infection by antibody patterns. *Pediatr Infect Dis J.* 1995;14(10):850-852.

48. Sohn AH, Thanh TC, Thinh le Q, et al. Failure of human immunodeficiency virus enzyme immunoassay to rule out infection among polymerase chain reaction-negative Vietnamese infants at 12 months of age. *Pediatr Infect Dis J*. 2009;28(4):273-276.

Laboratory Monitoring of Pediatric HIV Infection (Updated August 16, 2010)

***Panel's Recommendations*:**

- ***The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or count and plasma HIV RNA level (AII). For any given CD4 percentage or count, younger children, especially those in the first year of life, face higher risk of progression than do older children.***
- ***In children younger than 5 years of age, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group (AII).***
- ***CD4 percentage or count should be measured at the time of diagnosis of HIV infection and at least every 3–4 months thereafter (AIII).***
- ***Plasma HIV RNA should be measured to assess viral load at the time of diagnosis of HIV infection and at least every 3–4 months thereafter (AIII).***
- ***More frequent CD4 cell and plasma HIV RNA monitoring should be considered in infants younger than 6–12 months of age; in children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy (AIII).***
- ***An ultrasensitive viral load assay should be used to confirm that antiretroviral therapy is producing maximal suppression of viremia (AIII).***

IMMUNOLOGIC MONITORING IN CHILDREN

Clinicians interpreting CD4 count for children must consider age as a variable. CD4 count and percentage values in healthy infants who are not infected with HIV are considerably higher than values observed in uninfected adults and slowly decline to adult values by age 5 years *[1-2]*. In children younger than 5 years of age, the absolute CD4 count tends to vary more with age within an individual child than does CD4 percentage. Therefore, in HIV-infected children younger than 5 years of age, CD4 percentage is preferred for monitoring immune status, whereas absolute CD4 count can be used in older children *[3-5]*.

In HIV-infected children, as in infected adults, the CD4 count and percentage decline as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values (**Tables 3–5**). Consequently, CD4 values should be obtained as soon as possible after a child has a positive test for HIV and subsequently every 3–4 months. Increased frequency of evaluations may be needed for children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy. Because young infants with HIV infection may have rapid disease progression *[6-7]*, some experts monitor CD4 percentage more frequently (e.g., every 1–2 months) in untreated infants younger than 6 to 12 months of age. Because of the risk of rapid progression, initiation of antiretroviral treatment is now recommended for all HIV-infected infants younger than 12 months of age (see **When to Initiate Therapy in Antiretroviral-Naïve Children**). For adolescents who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2–3 years, some experts monitor CD4 counts and HIV RNA levels less frequently.

The prognostic value of CD4 percentage and HIV RNA copy number was assessed in a large individual patient meta-analysis (the HIV Pediatric Prognostic Markers Collaborative Study), which incorporated clinical and laboratory data from 17 pediatric studies and included 3,941 HIV-infected children receiving either no therapy or only zidovudine monotherapy *[4]*. The analysis looked at the short-term (12-month) risk of developing AIDS or death based on the child's age and selected values of CD4 percentage and HIV RNA copy number at baseline. **Figures 1 and 2** and **Table 3** depict age-associated 1-year risk of developing AIDS or death as a function of CD4 percentage. In a separate analysis of this data set, predictive value of absolute CD4 cell count for risk of death or AIDS/death in HIV-infected children 5 years of age or older was similar to that observed in

young adults, with an increase in the risk of mortality when CD4 cell count fell less than 350 cells/mm^3 (**Table 4** and **Figure 3**) *[3, 8]*.

The risk of disease progression associated with a specific CD4 percentage or count varies with the age of the child. Infants in the first year of life experience higher risks of progression or death than older children for any given CD4 stratum. For example, comparing a 1-year-old child with CD4 percentage of 25% to a 5-year-old child with the same CD4 percentage, there is an approximately fourfold increase in the risk of AIDS and sixfold increase in the risk of death in the 1-year-old child (**Figures 1 and 2**). Children 5 years of age or older have a lower risk of progression than younger children, with the increase in risk of AIDS or death corresponding to absolute CD4 levels more similar to those in young adults (**Figure 3**). In the HIV Pediatric Prognostic Marker Collaborative Study, there were no deaths among children 5 years of age or older with CD4 count greater than 350 cells/mm^3, although in younger children there continued to be a significant risk of death even with a CD4 cell count greater than 500 cells/mm^3 (**Table 4**).

These risk profiles form the rationale for recommendations on when to initiate therapy in a treatment-naïve HIV-infected child (see **When to Initiate Therapy in Antiretroviral-Naïve Children**). A Web site using the meta-analysis from the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) is available to estimate the short-term risk of progression to AIDS or death in the absence of effective antiretroviral therapy according to age and the most recent CD4 percentage or HIV-1 RNA viral load measurement (**http://hppmcs.org**) *[4]*.

Measurement of CD4 values can be associated with considerable intrapatient variation *[5]*. Even mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in CD4 count and percentage; thus, CD4 values are best measured when patients are clinically stable. No modification in therapy should be made in response to a change in CD4 values until the change has been substantiated by at least a second determination, with a minimum of 1 week between measurements.

HIV RNA MONITORING IN CHILDREN

Viral burden in peripheral blood can be determined by using quantitative HIV RNA assays. During the period of primary infection in adults, HIV RNA copy number initially rises to high peak levels and then declines by as much as 2–3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6–12 months following acute infection *[9-10]*. In infected adults, the viral set point correlates with the subsequent risk of disease progression or death *[11-12]*. On the basis of data from studies in infected adults, recommendations for the use of HIV RNA copy number in managing antiretroviral therapy have been developed for adults *[13]*. These recommendations also are applicable to infected adolescents.

The HIV RNA pattern in perinatally infected infants differs from that in infected adults and adolescents. High HIV RNA copy numbers persist in infected children for prolonged periods *[14-15]*. In one prospective study, HIV RNA levels generally were low at birth (i.e., <10,000 copies/mL), increased to high values by age 2 months (most infants had values >100,000 copies/mL, ranging from undetectable to nearly 10 million copies/mL), and then decreased slowly; the mean HIV RNA level during the first year of life was 185,000 copies/mL *[16]*. Additionally, in contrast to the adult pattern, after the first year of life, HIV RNA copy number slowly declines over the next few years *[16-19]*. This pattern probably reflects the lower efficiency of an immature, but developing, immune system in containing viral replication and possibly the rapid expansion of HIV-susceptible cells that occurs with somatic growth *[20]*.

High HIV RNA levels (i.e., >299,000 copies/mL) in infants age <12 months have been correlated with disease progression and death, but RNA levels overlap considerably in young infants who have rapid disease progression and those who do not *[14, 16]*. High RNA levels (i.e., levels of >100,000 copies/mL) in older children have also been associated with high risk of disease progression and mortality, particularly if CD4 percentage is <15% (**Table 5**) *[18-19]*. The most robust data set available to elucidate the predictive value of plasma RNA for disease progression in children was assembled in the HIV Pediatric Prognostic Markers Collaborative Study (see **Immunologic Monitoring in Children**) *[4]*. As for CD4 percentage, analyses were performed for age-associated risk in the context of plasma RNA levels in a cohort of children receiving either

no therapy or only zidovudine monotherapy. Similar to data from previous studies *[18-19]*, the risk of clinical progression to AIDS or death dramatically increases when HIV RNA exceeds 100,000 copies (5.0 $\log_{10}$ copies)/mL; at lower values, only older children show much variation in risk (**Figures 4 and 5** and **Table 3**). At any given level of HIV RNA, infants younger than 1 year of age were at higher risk of progression than older children, although these differences were less striking than those observed for the CD4 percentage data.

Despite data indicating that high plasma HIV RNA concentrations are associated with disease progression, the predictive value of specific HIV RNA concentrations for disease progression and death for an individual child is moderate *[18]*. HIV RNA concentration may be difficult to interpret during the first year of life because values are high and are less predictive of disease progression risk than in older children *[15]*. In both HIV-infected children and adults, CD4 percentage or count and HIV RNA copy number are independent predictors of disease progression and mortality risk, and use of the two markers together more accurately defines prognosis *[18-19, 21-23]*.

HIV RNA copy number should be assessed as soon as possible after a child has a positive virologic test for HIV and every 3–4 months thereafter; increased frequency of evaluations may be needed for children experiencing virologic, immunologic, or clinical deterioration; to confirm an abnormal value; or when initiating or changing antiretroviral therapy (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**). Because young infants with HIV infection may have rapid disease progression, some experts monitor HIV RNA concentration more frequently (e.g., every 1–2 months) in untreated infants younger than 6–12 months of age.

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays

The use of HIV RNA assays for clinical purposes requires specific considerations *[24]*, which are discussed more completely elsewhere *[13]*. Several different methods can be used for quantitating HIV RNA, each has a different level of sensitivity. Although the results of the assays are correlated, the absolute HIV RNA copy number obtained from a single specimen tested by two different assays can differ by twofold (0.3 $\log_{10}$ units) or more *[25-28]*.

There are currently five FDA-approved viral load assays using one of three different methodologies:

- HIV-1 reverse transcriptase (RT) quantitative PCR assays: the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics), for which the lower limit of detection differs between the "ultrasensitive" assay (<50 copies/mL) and the "regular sensitivity" assay (<400 copies/mL); the AmpliPrep/TaqMan HIV-1 Test (Roche Diagnostics); and the Real Time HIV-1 Assay (Abbott Molecular Incorporated);
- HIV-1 nucleic acid sequence-based amplification test (NucliSens HIV-1 QT, bioMerieux); and
- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (bDNA) (VERSANT HIV-1 RNA 3.0 Assay, Bayer).

The lower limits of detection of the assays differ (<40 copies/mL for the Abbott Real Time HIV-1 test, <48 copies/mL for the AmpliPrep/TaqMan HIV-1 Test, <50 copies/mL for the Amplicor HIV-1 Monitor Test, <80 copies/mL for the NucliSens HIV-1 QT assay, and <75 copies/mL for the VERSANT assay). Use of ultrasensitive viral load assays to confirm that antiretroviral therapy is producing maximal suppression of viremia is recommended. Because of the variability of assay techniques and quantitative HIV RNA measurements between these assays, a single HIV RNA assay method should be used consistently for monitoring an individual patient, if possible.

The predominant virus subtype in the United States is B, which is the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes, with the exception of the uncommon O subtypes *[29-30]*. This is important for many regions of the world where non-B subtypes are predominant, as well as for the United States, where a small subset of individuals are infected with non-B viral subtypes *[31-33]*. Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NucliSens assay requires the

least amount of blood (100 µL of plasma), followed by the RT PCR assays such as Amplicor HIV-1 Monitor (200 µL of plasma) and the VERSANT assays (1 mL of plasma).

Biologic variation in HIV RNA levels within one person is well documented. In adults, repeated measurement of HIV RNA levels using the same assay can vary by as much as threefold (0.5 $\log_{10}$) in either direction over the course of a day or on different days *[13, 21, 27]*. This biologic variation may be greater in infected infants and young children. In children with perinatally acquired HIV infection, RNA copy number slowly declines even without therapy during the first several years after birth, although it persists at higher levels than those observed in most infected adults *[16-18]*. This decline is most rapid during the first 12–24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ per year; a slower decline continues until approximately 4–5 years of age (average decline of 0.3 $\log_{10}$ per year).

This inherent biologic variability must be considered when interpreting changes in RNA copy number in children. Thus, only changes after repeated testing greater than fivefold (0.7 $\log_{10}$) in infants younger than 2 years of age and greater than threefold (0.5 $\log_{10}$) in children 2 years of age and older should be considered reflective of a biologically and clinically substantial change.

No alteration in therapy should be made as a result of a change in HIV copy number unless the change is confirmed by a second measurement. Because of the complexities of HIV RNA testing and the age-related changes in HIV RNA in children, interpretation of HIV RNA levels for clinical decision making should be done by or in consultation with an expert in pediatric HIV infection.

Table 3. Likelihood of Developing AIDS or Death Within 12 Months, by Age and $CD4^+$ T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**25%**	**30%**	**6.0**	**5.0**	**4.0**
Percent Mortality (95% Confidence Interval)							
6 Months	28.7	12 .4	8.5	6.4	9.7	4.1	2.7
1 Year	19.5	6.8	4.5	3.3	8.8	3.1	1.7
2 Years	11.7	3.1	2.0	1.5	8.2	2.5	1.1
5 Years	4.9	0.9	0.6	0.5	7.8	2.1	0.7
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51.4	31.2	24.9	20.5	23.7	13.6	10.9
1 Year	40.5	20.9	15.9	12.8	20.9	10.5	7.8
2 Years	28.6	12 .0	8.8	7.2	18.8	8.1	5.3
5 Years	14.7	4.7	3.7	3.1	17.0	6.0	3.2
10 Years	7.4	2.2	1.9	1.8	16.2	5.1	2.2

Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet* 2003; 362:1605-11.

Table 4. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)*

Age (Years)	Absolute CD4 cell count (cells/mm^3)					
	<50	**50–99**	**100–199**	**200–349**	**350–499**	**500+**
Rate of Death Per 100 Patient-Years						
0–4	59.3	39.6	25.4	11.1	10.0	3.5
5–14	28.9	11.8	4.3	0.89	0.00	0.00
15–24	34.7	6.1	1.1	0.71	0.58	0.65
25–34	47.7	10.8	3.7	1.1	0.38	0.22
35–44	58.8	15.6	4.5	0.92	0.74	0.85
45–54	66.0	18.8	7.7	1.8	1.3	0.86
55+	91.3	21.4	17.6	3.8	2.5	0.91
Rate of AIDS or Death per 100 Patient-Years						
0–4	82.4	83.2	57.3	21.4	20.7	14.5
5–14	64.3	19.6	16.0	6.1	4.4	3.5
15–24	61.7	30.2	5.9	2.6	1.8	1.2
25–34	93.2	57.6	19.3	6.1	2.3	1.1
35–44	88.1	58.7	25.5	6.6	4.0	1.9
45–54	129.1	56.2	24.7	7.7	3.1	2.7
55+	157.9	42.5	30.0	10.0	5.1	1.8

* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008;197:398-404.

Table 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4+ T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children*

Baseline HIV RNA§ (copies/mL)/Baseline CD4+ T-cell percentage	No. patients¶	Deaths†	
		No.	(%)
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

† Mean follow-up: 5.1 years.

§ Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

¶ Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *J Infect Dis*, 1997. 175(5):1029–38.

Figure 1. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

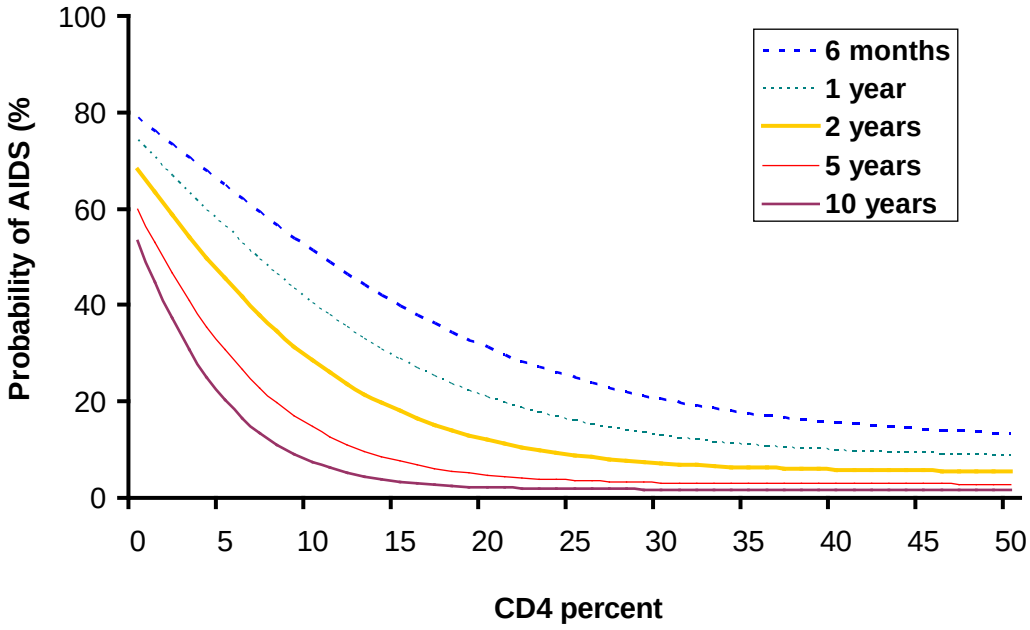


Figure 2. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

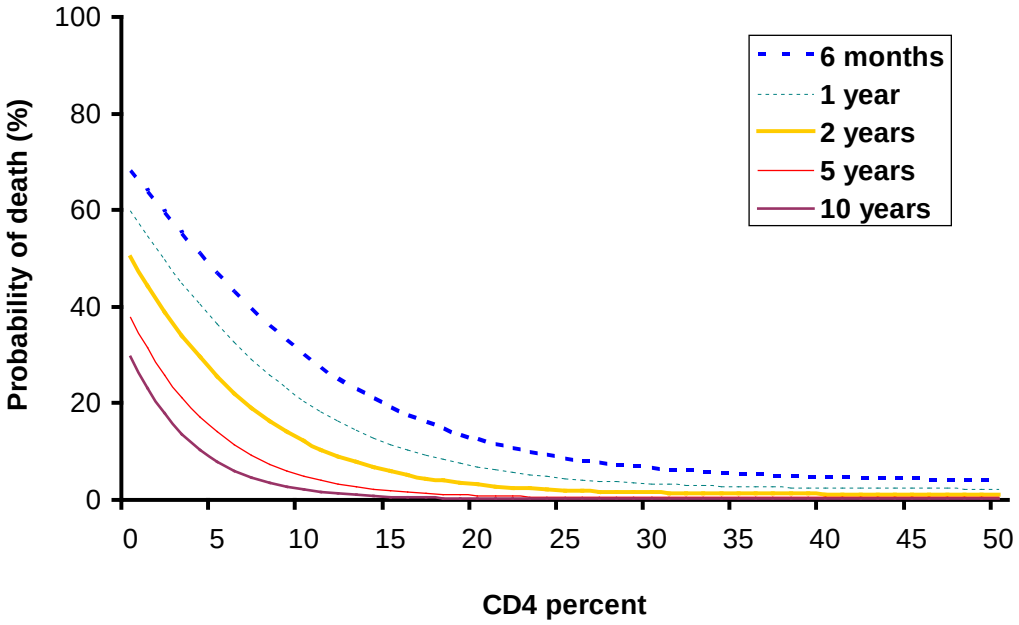
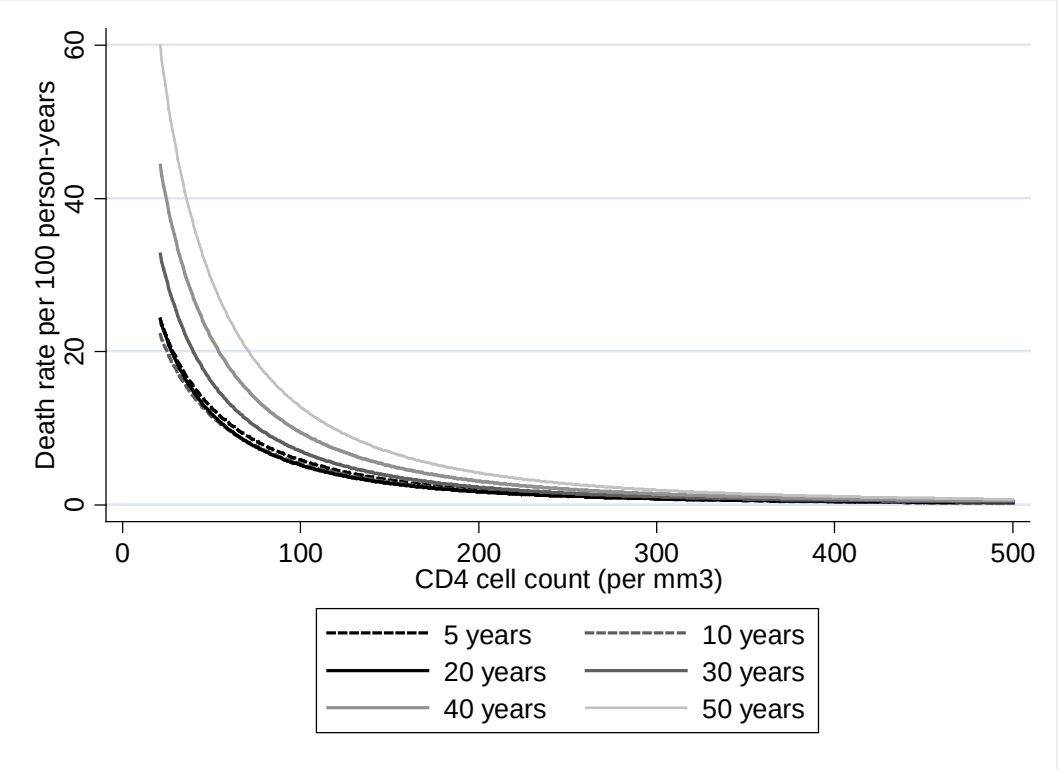


Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*



* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008;197:398-404.

Figure 4. Estimated Probability of AIDS Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

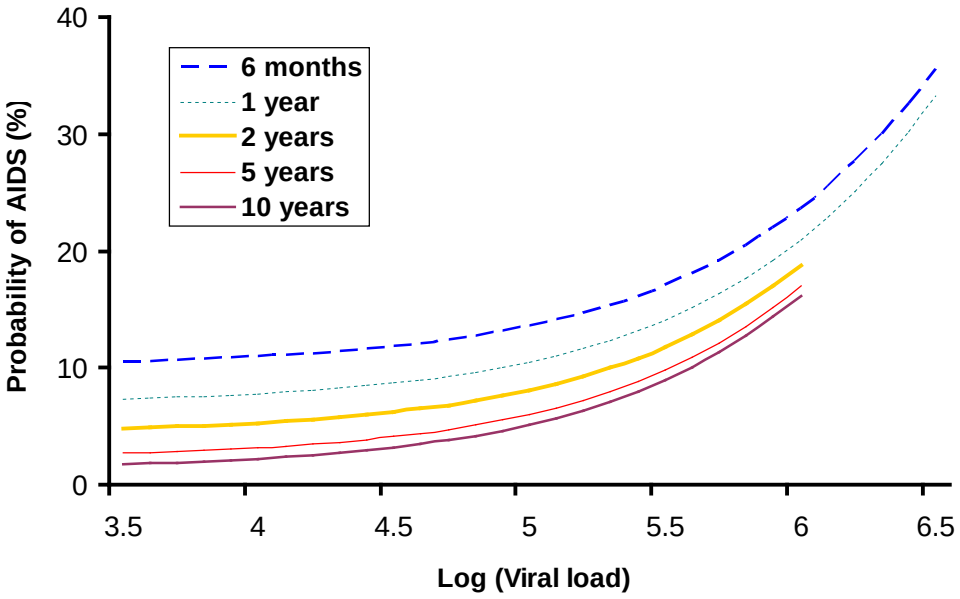
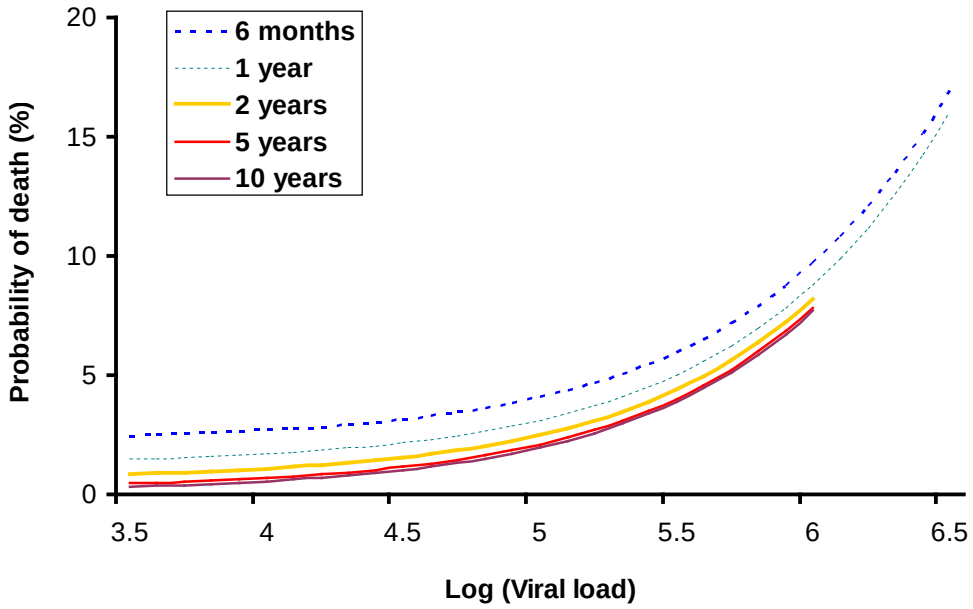


Figure 5. Estimated Probability of Death Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*



References

1. European Collaborative Study. Age-related standards for T lymphocyte subsets based on uninfected children born to human immunodeficiency virus 1-infected women. The European Collaborative Study. *Pediatr Infect Dis J.* 1992;11(12):1018-1026.
2. Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol.* 2003;112(5):973-980.
3. HIV Paediatric Prognostic Markers Collaborative Study. Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. *AIDS.* 2006;20(9):1289-1294.
4. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet.* 2003;362(9396):1605-1611.
5. Raszka WV, Jr., Meyer GA, Waecker NJ, et al. Variability of serial absolute and percent CD4+ lymphocyte counts in healthy children born to human immunodeficiency virus 1-infected parents. Military Pediatric HIV Consortium. *Pediatr Infect Dis J.* 1994;13(1):70-72.
6. Simonds RJ, Lindegren ML, Thomas P, et al. Prophylaxis against Pneumocystis carinii pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States. Pneumocystis carinii Pneumonia Prophylaxis Evaluation Working Group. *N Engl J Med.* 1995;332(12):786-790.
7. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
8. Dunn D, Woodburn P, Duong T, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis.* 2008;197(3):398-404.
9. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA.* 1995;274(7):554-558.
10. Katzenstein TL, Pedersen C, Nielsen C, et al. Longitudinal serum HIV RNA quantification: correlation to viral phenotype at seroconversion and clinical outcome. *AIDS.* 1996;10(2):167-173.
11. Clementi M, Menzo S, Bagnarelli P, et al. Clinical use of quantitative molecular methods in studying human immunodeficiency virus type 1 infection. *Clin Microbiol Rev.* 1996;9(2):135-147.
12. Mellors JW, Kingsley LA, Rinaldo CR, Jr., et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med.* 1995;122(8):573-579.
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
14. Abrams EJ, Weedon J, Steketee RW, et al. Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants. New York City Perinatal HIV Transmission Collaborative Study Group. *J Infect Dis.* 1998;178(1):101-108.
15. Palumbo PE, Kwok S, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *J Pediatr.* 1995;126(4):592-595.
16. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med.* 1997;336(19):1337-1342.
17. McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. *Pediatr Infect Dis J.* 1996;15(12):1087-1091.
18. Mofenson LM, Korelitz J, Meyer WA, 3rd, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis.* 1997;175(5):1029-1038.
19. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA.* 1998;279(10):756-761.
20. Krogstad P, Uittenbogaart CH, Dickover R, et al. Primary HIV infection of infants: the effects of somatic growth on lymphocyte and virus dynamics. *Clin Immunol.* 1999;92(1):25-33.
21. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med.* 1997;126(12):929-938.

22. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.
23. O'Brien WA, Hartigan PM, Daar ES, et al. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. *Ann Intern Med.* 1997;126(12):939-945.
24. Reichelderfer PS, Coombs RW. Virologic parameters as surrogate markers for clinical outcome in HIV-1 disease: verification, variation, and validation. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;10 Suppl 2:S19-24.
25. Brambilla D, Leung S, Lew J, et al. Absolute copy number and relative change in determinations of human immunodeficiency virus type 1 RNA in plasma: effect of an external standard on kit comparisons. *J Clin Microbiol.* 1998;36(1):311-314.
26. Goetz M, Moatamed F, Howanitz J. Measurement of plasma HIV viral load (VL) by bDNA versus RT PCR (PCR) assays. *Clin Infect Dis.* 1997;25(394):Abstract 207.
27. Raboud JM, Montaner JS, Conway B, et al. Variation in plasma RNA levels, CD4 cell counts, and p24 antigen levels in clinically stable men with human immunodeficiency virus infection. *J Infect Dis.* 1996;174(1):191-194.
28. Vandamme AM, Schmit JC, Van Dooren S, et al. Quantification of HIV-1 RNA in plasma: comparable results with the NASBA HIV-1 RNA QT and the AMPLICOR HIV monitor test. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;13(2):127-139.
29. Antunes R, Figueiredo S, Bartolo I, et al. Evaluation of the clinical sensitivities of three viral load assays with plasma samples from a pediatric population predominantly infected with human immunodeficiency virus type 1 subtype G and BG recombinant forms. *J Clin Microbiol.* 2003;41(7):3361-3367.
30. Plantier JC, Gueudin M, Damond F, et al. Plasma RNA quantification and HIV-1 divergent strains. *J Acquir Immune Defic Syndr.* 2003;33(1):1-7.
31. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infect Dis.* 1996;174(1):244-245.
32. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J.* 2002;21(9):885-886.
33. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis.* 2002;34(3):417-418.

Treatment Recommendations (Updated August 16, 2010)

GENERAL CONSIDERATIONS

Treatment of pediatric HIV infection in the United States has evolved since antiretroviral therapy began in the late 1980s. Prior to the availability of antiretroviral drugs for children, care focused on prevention and management of HIV-related complications and provision of palliative care. Initial studies of monotherapy in children in the early 1990s demonstrated significant clinical and immunologic benefit with treatment *[1-4]*; further research demonstrated that combination therapy (initially dual-NRTI treatment) led to better clinical, immunologic, and virologic outcomes than monotherapy *[5]*. Currently, highly active combination regimens including at least three drugs are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children *[6-10]*. In the United States and the United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens *[11-12]*; significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period *[10, 12]*.

The increased survival of HIV-infected children is associated with challenges in selecting successive new antiretroviral drug regimens. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be recognized in children *[13-14]*.

Antiretroviral drug-resistant virus can develop in both multidrug experienced children and children who received initial regimens containing one or two drugs that incompletely suppressed viral replication. Additionally, drug resistance may be seen in antiretroviral-naïve children who have become infected with HIV despite maternal/infant antiretroviral prophylaxis *[15-16]*. Thus, decisions about when to start therapy and what drugs to choose in antiretroviral-naïve children and on how to best treat antiretroviral-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by or made in consultation with a specialist in pediatric and adolescent HIV infection. Treatment of antiretroviral-naïve children (when and what to start), when to change therapy, and treatment of antiretroviral-experienced children will be discussed in separate sections of the guidelines.

A number of factors need to be considered in making decisions about initiating and changing antiretroviral therapy in children, including:

- severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see pediatric clinical staging system for HIV, **Table 6**) *[17-18]*, level of CD4 cell immunosuppression, and magnitude of HIV plasma viremia;
- availability of appropriate (and palatable) drug formulations and pharmacokinetic information on appropriate dosing in the child's age group;
- potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the antiretroviral regimen;
- effect of initial regimen choice on later therapeutic options;
- presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect drug choice;
- potential antiretroviral drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by the child; and
- the ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although

prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from Phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

GOALS OF ANTIRETROVIRAL TREATMENT

Current antiretroviral therapies do not eradicate HIV infection due to the long half-life of latently infected CD4 cells *[19-21]*; some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 months vs. 5–10 months, respectively) *[21]*. Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of antiretroviral therapy for HIV-infected children include:

- reducing HIV-related mortality and morbidity;
- restoring and/or preserving immune function;
- maximally and durably suppressing viral replication;
- minimizing drug-related toxicity;
- maintaining normal physical growth and neurocognitive development; and
- improving quality of life.

Strategies to achieve these goals require complex balancing of sometimes competing considerations.

Use and selection of combination antiretroviral therapy: At present, the treatment of choice for HIV-infected children is at least three drugs, which include at least two classes of antiretroviral drugs. The Panel has recommended several preferred and alternative regimens (see **What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children**). The most appropriate regimen for an individual child depends on multiple factors, including age of the child and availability of appropriate drug formulations; the potency, complexity, and toxicity of the regimen; the child and caregiver's ability to adhere to the regimen; the child's home situation; and the child's antiretroviral treatment history.

Drug sequencing and preservation of future treatment options: The choice of antiretroviral treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in antiretroviral drug regimens can rapidly exhaust treatment options and should be avoided unless required (e.g., severe toxicity or intolerance or significant clinical, immunologic, or virologic progression). Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Currently, recommendations for initial therapy are to use two classes of drugs—two NRTIs combined with either an NNRTI or a PI—thereby sparing three classes of drugs for later use.

Maximizing adherence: As discussed in **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents**, lack of adherence to prescribed regimens can lead to subtherapeutic levels of antiretroviral medications, which enhances the risk of the development of drug resistance and likelihood of virologic failure. Participation by the caregivers and child in the decision-making process is crucial. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with the child's caregiver and the child (when age appropriate) before the decision to initiate therapy is made. Potential problems should be identified and resolved prior to starting therapy, even if this delays initiation of therapy. Additionally, frequent follow-up is important to provide assessment of virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence before making changes to the antiretroviral regimen.

Table 6. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories*

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly Symptomatic

Children with **two** or more of the following conditions but none of the conditions listed in Categories B and C:

- Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following:

- Anemia (<8 gm/dL), neutropenia (<1,000 cells/mm^3), or thrombocytopenia (<100,000 cells/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children age >6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting >1 month
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (below), with the exception of LIP (which is a Category B condition):

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **PLUS** 1) chronic diarrhea (i.e., ≥ two loose stools per day for >30 days), **OR** 2) documented fever (for ≥30 days, intermittent or constant)

* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*, 1994. 43 (No. RR-12): p. 1–10.

References

1. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med.* 1991;324(3):137-144.
2. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch-Human Immunodeficiency Virus Working Group. *J Infect Dis.* 1996;174(1):16-25.
3. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med.* 1991;324(15):1018-1025.
4. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.
5. Resino S, Resino R, Micheloud D, et al. Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. *Clin Infect Dis.* 2006;42(6):862-869.
6. Lindsey JC, Malee KM, Brouwers P, et al. Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy. *Pediatrics.* 2007;119(3):e681-693.
7. Nachman SA, Lindsey JC, Moye J, et al. Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J.* 2005;24(4):352-357.
8. Paediatric European Network for Treatment of Aids (PENTA). Five year follow up of vertically HIV infected children in a randomised double blind controlled trial of immediate versus deferred zidovudine: the PENTA 1 trial. *Arch Dis Child.* 2001;84(3):230-236.
9. Storm DS, Boland MG, Gortmaker SL, et al. Protease inhibitor combination therapy, severity of illness, and quality of life among children with perinatally acquired HIV-1 infection. *Pediatrics.* 2005;115(2):e173-182.
10. Viani RM, Araneta MR, Deville JG, et al. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2004;39(5):725-731.
11. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr.* 2010;53(1):86-94.
12. Judd A, Doerholt K, Tookey PA, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clin Infect Dis.* 2007;45(7):918-924.
13. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.
14. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
15. Delaugerre C, Chaix ML, Blanche S, et al. Perinatal acquisition of drug-resistant HIV-1 infection: mechanisms and long-term outcome. *Retrovirology.* 2009;6:85.
16. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
17. Centers for Disease Control and Prevention (CDC). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(RR-12):1-10.
18. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
19. Persaud D, Siberry GK, Ahonkhai A, et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J Virol.* 2004;78(2):968-979.
20. Pomerantz RJ. Residual HIV-1 infection during antiretroviral therapy: the challenge of viral persistence. *AIDS.* 2001;15(10):1201-1211.
21. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.

When to Initiate Therapy in Antiretroviral-Naïve Children (Updated August 16, 2010)

The choice of whether to start therapy early, while an individual is still asymptomatic, versus delaying therapy until clinical or immunologic deterioration occurs continues to generate considerable controversy among HIV experts. Some experts favor starting aggressive therapy in the early stages of HIV infection in the hope that early antiretroviral intervention will control viral replication prior to the onset of rapid genetic mutation and evolution into multiple quasi-species. This could result in a lower viral set point, fewer mutant viral strains, and potentially less drug resistance. Early therapy would slow immune system destruction and preserve immune function, preventing clinical disease progression. On the other hand, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, greater adherence to the therapeutic regimen when the patient is symptomatic rather than asymptomatic, and reduced or delayed adverse effects of antiretroviral therapy.

Recommendations for when to initiate therapy have generally been more aggressive in children than adults because HIV infection is primarily transmitted from mother to child, thereby allowing identification of the timing of infection in children; HIV disease progression in children is more rapid than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for young infants. As discussed in **Laboratory Monitoring of Pediatric HIV Infection**, CD4 count and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children younger than 12 months. Hence, recommendations for when to start therapy differ by age of the child. As discussed earlier, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, CD4 percentage and HIV RNA levels were both independently predictive of the risk of clinical progression or death in children older than 12 months, although CD4 percentage was a stronger predictor of risk than HIV RNA levels *[1]*. Based on data showing that surrogate marker-based risk of progression varies considerably by age but that CD4 count-associated risk of progression in children age 5 years or older is similar to young adults, the Panel has moved to recommendations for three age bands for initiation of treatment: infants younger than age 12 months, children age 1 to <5 years, and children and adolescents age ≥5 years.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED INFANTS YOUNGER THAN AGE 12 MONTHS

Panel's Recommendations (Table 7):

- ***Initiation of antiretroviral therapy is recommended for infants age <12 months, regardless of clinical status, CD4 percentage, or viral load (AI).***
- ***Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated (AIII).***

Data from the South African CHER Trial (Children with HIV Early Antiretroviral Therapy) demonstrated that initiation of triple-drug antiretroviral therapy prior to 12 weeks of age in asymptomatic perinatally infected children with normal CD4 percentage (CD4 >25%), compared with waiting to start treatment until the child met clinical or immune criteria, resulted in a 75% reduction in early mortality*[2]*. Most of the deaths in the children in the delayed arm occurred in the first 6 months after study entry. Because the risk of rapid progression is so high in young infants and based on the data from the CHER study, the Panel recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage, or viral load (**Table 7**). It is critical that issues associated with adherence are fully assessed and discussed with the HIV-infected infant's caregivers and addressed before therapy is initiated.

The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in infected infants; by 12 months of age, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression *[3]*. In the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger than in older children at any given level of CD4 percentage, particularly for infants age <12 months *[4]*. Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections can occur in young infants with normal CD4 counts *[4]*.

Identification of HIV infection during the first few months of life permits clinicians to initiate antiretroviral therapy during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who started therapy later. Analyses from a prospective study of 360 HIV-infected children in the United States (Perinatal AIDS Collaborative Transmission Study [PACTS]) showed that infants who received early treatment (prior to age 2 years, with nearly half starting in the first year of life) were significantly less likely to progress to AIDS or death compared with those who received no therapy, adjusting for year of birth and maternal disease factors *[5]*. In the European Infant Collaboration Group, starting antiretroviral therapy before the age of 3 months was associated with a significant reduction in progression to AIDS or death compared with deferring therapy *[6]*. In an analysis from the European Collaborative Study, HIV-infected children who initiated potent therapy before age 5 months were more likely to achieve CD4 recovery (defined as 20% increase in CD4 *z* score) than children initiating therapy at older ages *[7]*.

Several small studies have demonstrated that despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, there has also been lack of detection of extra-chromosomal replication intermediates, suggesting near-complete control of viral replication. Some of these infants have become HIV seronegative and have lost HIV-specific immune responses. However, therapy is not curative; proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued *[8-9]*.

There are, however, potential problems with treatment of asymptomatic infants. Virologic suppression may take longer in young children (given their higher viral load at the time of initiation of therapy) than in older children or adults *[10]*, and the rates of virologic failure with therapy started early in life may be higher than when started later *[11]*. Incomplete viral suppression can lead to the development of drug resistance and compromise future treatment options *[12]*. Possible reasons for the poor response in infants include very high viral loads in young infants, inadequate antiretroviral drug levels, and poor adherence due to the difficulties in administering complex regimens to infants. However, with currently available drug regimens, rates of viral suppression of 70%–80% have been reported in HIV-infected infants initiating therapy at age <12 months *[13-15]*. In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at age <6 months, 98% had CD4 >25% and 78% had undetectable viral load with median follow-up of 5.96 years *[13]*.

Information on appropriate drug dosing in infants younger than age 3–6 months is limited. Hepatic and renal functions are immature in the newborn undergoing rapid maturational changes during the first few months of life which can result in substantial differences in antiretroviral dose requirements between young infants and older children. When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, antiretroviral drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. It is particularly critical to discuss fully the importance of treatment adherence with the caregivers and to identify and resolve potential problems prior to initiation of therapy, even if this delays starting treatment. Frequent follow-up and continued assessment and support of adherence are especially important in the treatment of young infants (see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents**).

Finally, the possibility of toxicities—such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction—with prolonged therapy is a concern *[16]*. Concerns about toxicities are particularly relevant because life-long administration of therapy may be necessary. Whether it might be possible to stop therapy begun in early infancy after a defined period of treatment (e.g., 1–2 years) that protected the child during the period of greatest risk of HIV disease progression and mortality, and then restart therapy when the child meets standard age-related criteria, is under assessment in clinical trials in South Africa and Kenya.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED CHILDREN AGE 1 YEAR OR OLDER

Panel's Recommendations (Table 7):

- ***Initiation of antiretroviral therapy is recommended for children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level (AI*).***
- ***Initiation of antiretroviral therapy is also recommended for children age ≥1 year who have met the age-related CD4 threshold for initiating treatment (CD4 <25% for children age 1 to <5 years (AII) and <350 cells/mm^3 for children age ≥5 years (AI*), regardless of symptoms or plasma HIV RNA level).***
- ***Initiation of antiretroviral therapy is also recommended for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or the following Clinical Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) and have CD4 ≥25% for children age 1 to <5 years or ≥350 cells/mm^3 for children age ≥5 years and have plasma HIV RNA ≥100,000 copies/mL (BII).***
- ***Initiation of antiretroviral therapy may be considered or deferred for children age ≥1 year who are asymptomatic or have mild symptoms and who have CD4 ≥25% for children age 1 to <5 years and ≥350 cells/mm^3 for children age ≥5 years and have plasma HIV RNA <100,000 copies/mL (CIII).***

The risk of disease progression slows in children age ≥1 year. It is clear that children with clinical AIDS or significant symptoms (Clinical Category C or B—**Table 6**) *[17]* are at high risk of disease progression and death; treatment is recommended by the Panel for all such children, regardless of immunologic or virologic status. However, children age ≥1 year with mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than those with more severe clinical symptoms *[18]*. It should also be noted that some Clinical Category B conditions—a single episode of serious bacterial infection or lymphoid interstitial pneumonitis—are less prognostic of the risk of disease progression. Consideration of CD4 count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, considerations related to initiation of antiretroviral therapy are based primarily on risk of disease progression as determined by baseline CD4 count *[19]*. In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 count <350 cells/mm^3. In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 count fell to <350 cells/mm^3 compared with deferring treatment until CD4 count fell to <200 cell/mm^3*[20]*. In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003, the risk of AIDS or death was significantly less in those who started treatment with CD4 count of 200–350 cells/mm^3 compared with those who started at <200 cells/mm^3 *[21]*.

There are no randomized trial data to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults, the ART Cohort Collaboration (ART-CC) and NA-Accord, suggest a higher rate of progression to AIDS or death in patients deferring treatment until CD4 count <350 cells/mm^3 compared with starting when CD4 count was 351 to 450–500 cells/mm^3 *[22-23]*. However, although the relative risk was increased, the overall number of events was small. The NA-Accord study demonstrated a benefit of starting treatment when CD4 count was >500 cell/mm^3

compared with starting when CD4 fell below this threshold *[22]*; however the ART-CC cohort found no additional benefit for patients starting antiretroviral therapy with CD4 counts greater than 450 cells/mm^3 *[23]*. The HHS Adult Antiretroviral Guidelines Panel was split on recommendations regarding starting therapy in HIV-infected adults with CD4 count 350–500 cells/mm^3 (moderate to strong recommendation) and >500 cells/mm^3 (moderate recommendation to optional) *[19]*.

In children, the prognostic significance of a specific CD4 percentage or count varies with age *[4, 24]*. Data from pediatric studies also suggest the immune response to treatment in children is better when treatment is initiated at higher CD4 percentage/count levels *[11, 25]*. In data from the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count among children age 1–4 years than among children age ≥5 years (**Tables 3–4** and **Figures 1–2**). Data from the HIV Pediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children age ≥5 years, in whom the estimated risk of disease progression increases when the count falls below 350 cells/mm^3, similar to data in adults (**Table 4**) *[1, 4]*. For children age 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (**Table 3**).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count *[4]*. Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality *[26-27]*; similar data have been reported in adults *[28]*. Similarly, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children age >1 year when HIV RNA levels were ≥100,000 copies/mL (**Table 3** and **Figures 4–5**) *[4]*. For example, the estimated 1-year risk of death was 2–3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8–10 times higher if plasma HIV RNA was >1,000,000 copies/mL.

Based on these data, the Panel has the following recommendations for treatment of children age 1 to <5 years. Initiation of antiretroviral therapy is recommended for children age 1 to <5 years who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have a CD4 percentage <25%, regardless of clinical symptoms or HIV RNA level. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]) with CD4 percentage ≥25% if plasma HIV RNA is >100,000 copies/mL. Antiretroviral therapy may be considered or deferred in asymptomatic children age 1 to <5 years who have CD4 ≥25% and who also have plasma HIV RNA levels <100,000 copies/mL.

For children who are age 5 years or older, initiation of antiretroviral therapy is recommended if they have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have CD4 <350 cells/mm^3, regardless of clinical symptoms or HIV RNA level. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]) with CD4 ≥350 cells/mm^3 if HIV RNA is >100,000 copies/mL. Antiretroviral therapy may be considered or deferred for asymptomatic or mildly symptomatic children age ≥5 years who have CD4 ≥350 cells/mm^3 and who also have plasma HIV RNA levels <100,000 copies/mL.

If therapy is deferred, the health care provider should closely monitor virologic, immunologic, and clinical status (see **Laboratory Monitoring of Pediatric HIV Infection**). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL);
- Rapidly declining CD4 count or percentage to values approaching the age-related threshold for consideration of therapy;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed, and addressed with the child, if age appropriate, and the caregiver before the decision to initiate therapy is made.

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (AI)*
1–<5 years	• AIDS or significant HIV-related symptoms[1]	*Treat (AI*)*
	• CD4 <25%, regardless of symptoms or HIV RNA level	*Treat (AII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥25% *and* o HIV RNA ≥100,000 copies/mL	*Treat (BII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥25% *and* o HIV RNA <100,000 copies/mL	*Consider or Defer*[3] *(CIII)*
≥5 years	• AIDS or significant HIV-related symptoms[1]	*Treat (AI*)*
	• CD4 <350 cells/mm^3	*Treat (AI*)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA ≥100,000 copies/mL	*Treat (BII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA <100,000 copies/mL	*Consider or Defer*[3] *(CIII)*

[1] CDC Clinical Categories C and B (except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

[2] CDC Clinical Category A or N or the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

[3] Clinical and laboratory data should be re-evaluated every 3 to 4 months.

References

1. Dunn D, Woodburn P, Duong T, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis.* 2008;197(3):398-404.
2. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
3. Gray L, Newell ML, Thorne C, et al. Fluctuations in symptoms in human immunodeficiency virus-infected children: the first 10 years of life. *Pediatrics.* 2001;108(1):116-122.
4. HIV Paediatric Prognostic Markers Collaborative Study. Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. *AIDS.* 2006;20(9):1289-1294.
5. Abrams EJ, Wiener J, Carter R, et al. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS.* 2003;17(6):867-877.
6. Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS.* 2009;23(5):597-604.
7. Newell ML, Patel D, Goetghebuer T, et al. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis.* 2006;193(7):954-962.
8. Persaud D, Siberry GK, Ahonkhai A, et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J Virol.* 2004;78(2):968-979.
9. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.
10. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.
11. Walker AS, Doerholt K, Sharland M, et al. Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. *AIDS.* 2004;18(14):1915-1924.
12. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
13. Chiappini E, Galli L, Tovo PA, et al. Five-year follow-up of children with perinatal HIV-1 infection receiving early highly active antiretroviral therapy. *BMC Infect Dis.* 2009;9:140.
14. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
15. Van der Linden D, Hainaut M, Goetghebuer T, et al. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J.* 2007;26(4):359-361.
16. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
17. Centers for Disease Control and Prevention (CDC). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(RR-12):1-10.
18. Galli L, de Martino M, Tovo PA, et al. Predictive value of the HIV paediatric classification system for the long-term course of perinatally infected children. *Int J Epidemiol.* 2000;29(3):573-578.
19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
20. Severe P, Pape J, Fitzgerald D, et al. A randomized clinical trial of early versus standard antiretroviral therapy for HIV-infected patients with a CD4 T cell count of 200 - 350 cells/ml (CIPRAHT001). Paper presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy; September 12-15, 2009; San Francisco, CA.
21. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS.* 2007;21(9):1185-1197.
22. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med.* 2009;360(18):1815-1826.
23. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet.* 2009;373(9672):1352-1363.

24. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet.* 2003;362(9396):1605-1611.
25. Soh CH, Oleske JM, Brady MT, et al. Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet.* 2003;362(9401):2045-2051.
26. Mofenson LM, Korelitz J, Meyer WA, 3rd, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis.* 1997;175(5):1029-1038.
27. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA.* 1998;279(10):756-761.
28. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-129.

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children

(Updated August 16, 2010)

Panel's Recommendations:

- ***Antiretroviral drugs initiated for chemoprophylaxis of maternal-child HIV transmission should be discontinued in infants who are identified as HIV infected (AI) and treatment initiated with combination therapy as described below.***
- ***Antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children (AII infants; AIII children).***
- ***The goal of therapy in treatment-naïve children is to reduce plasma HIV RNA levels to below the limits of quantitation on ultrasensitive assays and to preserve or normalize immune status (AI).***
- ***Combination therapy with at least three drugs, including either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor plus a dual nucleoside analogue reverse transcriptase inhibitor backbone, is recommended for initial treatment of HIV-infected children (AI).***

GENERAL CONSIDERATIONS

As of August 2010, 22 antiretroviral drugs are approved for use in HIV-infected adults and adolescents; 17 of these have an approved pediatric treatment indication and 15 are available as a pediatric formulation or capsule size. These drugs fall into several major classes: nucleoside analogue or nucleotide analogue reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in **Appendix B: Pediatric Antiretroviral Drug Information**. It is likely that new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will become available over time, which will increase treatment options for children.

Combination antiretroviral therapy with at least three drugs from at least two classes of drugs is recommended for initial treatment of infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression *[1-4]*. The goal of antiretroviral therapy is to maximally suppress viral replication, preferably to undetectable levels, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used *[3-5]*.

Because antiretroviral therapy will need to be administered lifelong, considerations related to the choice of initial antiretroviral regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens; differing formulations; palatability problems; and potential limitations in subsequent treatment options should resistance develop.

Monotherapy and two-drug therapy with the currently available antiretroviral drugs are not recommended to treat HIV infection *[1, 6]*. Use of zidovudine as a single agent is appropriate only when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants confirmed as HIV infected while receiving chemoprophylaxis should have prophylactic antiretroviral drugs discontinued and treatment initiated with a combination regimen of at least 3 drugs (which may include zidovudine as part of the regimen if sensitive). The choice of regimen should be based on results from

antiretroviral drug resistance testing. Treatment should only be initiated following assessment and counseling of the caregivers regarding adherence to therapy *[1, 6]*.

Antiretroviral drug-resistance testing is recommended prior to the initiation of therapy in all treatment-naïve children. Treatment-naïve children with perinatal HIV infection can acquire drug-resistant virus from their mothers (because the mothers were initially infected with drug-resistant virus or acquired drug resistance during treatment or during use of antiretroviral drugs for prevention of mother-to-child transmission of HIV [PMTCT]), or the infant can develop resistance during the period of infant antiretroviral prophylaxis prior to diagnosis of HIV infection. Drug-resistant virus has been identified in 6%–16% of antiretroviral-naïve adults and 18% of behaviorally infected adolescents with recent infection in United States and Europe *[7-11]*. Data from children are limited. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and 19% of 42 infants born from 2000 to 2001 *[12-13];* detection of resistance in the infants was not signficantly associated with a history of maternal and infant antiretroviral prophylaxis. Similarly, following initiation of treatment, 24% of 21 infants (median age 9.7 weeks) were found to have mutations associated with drug resistance, most of which were not associated with maternal/infant prophylaxis regimens; resistant virus was found to be persistently archived in the resting CD4 cell reservoir *[14]*. Thus, the prevalence of infants infected with antiretroviral drug-resistant virus may be increasing and may not necessarily be predicted by the drug prophylaxis regimen received by the mother. In a recent trial, pretreatment detection of nevirapine resistance mutations was associated with a significantly higher rate of virologic failure of a nevirapine-based regimen among infants exposed to peripartum nevirapine used as maternal-infant prophylaxis *[15]*. For antiretroviral-naïve children beyond infancy, limited available data do not demonstrate that resistance testing prior to initiation of therapy correlates with greater success of initial antiretroviral therapy *[16]*. Nevertheless, the prevalence of resistance in HIV-infected children is sufficiently high that, based on expert opinion, the Panel recommends resistance testing prior to initiation of therapy in all treatment-naïve children and use of resistance testing results to refine selection of drugs for inititial combination therapy, similar to recommendations for HIV-infected adults *[17]*. Infants exposed to peripartum nevirapine as part of maternal-infant prophylaxis should not use nevirapine-based regimens for initial combination therapy, even if baseline resistance testing with standard commercial assays fails to demonstrate mutations associated with nevirapine resistance because the presence of minor resistance variants may be associated with virologic failure of NNRTI-based therapy *[18]*.

REGIMENS RECOMMENDED FOR INITIAL THERAPY OF ANTIRETROVIRAL-NAÏVE CHILDREN (TABLES 8 AND 9)

Criteria Used for Recommendations

There are few randomized, Phase III clinical trials of combination antiretroviral therapy among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from Phase I/II safety and pharmacokinetic trials and nonrandomized, open-label studies. The Panel reviews both pediatric and adult clinical trial data published in peer-reviewed journals, data prepared by manufacturers for FDA review, and data presented in abstract format at major scientific meetings. In general, even in studies in adults, assessment of efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 cell count and HIV RNA levels. Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized.

Criteria used by the Panel for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;

- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size and number;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions.

Drugs or drug combinations are classified in one of several categories as follows:

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use, and studies have been performed to demonstrate safety and surrogate marker efficacy in children; additional considerations are listed above.
- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- ***Use in Special Circumstances:*** Some drugs or drug combinations are recommended for use as initial therapy only in special circumstances, when preferred or alternative drugs cannot be used.
- ***Not Recommended:*** A list of drugs and drug combinations that are not recommended for initial therapy in children is shown in **Table 9**. These drugs and drug combinations are not recommended either because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism.
- ***Insufficient Data to Recommend:*** For a number of drugs and drug combinations approved for use in adults, pharmacokinetic or safety data in children are not available or are too limited to make recommendation on use of the drugs as initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in the management of the treatment-experienced child, even though they are not recommended for initial therapy in children (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: NNRTI based (two NRTIs plus an NNRTI); PI based (two NRTIs plus a PI); and NRTI only (three NRTI drugs). NNRTI- or PI-based regimens are preferred for initial therapy; decisions about which type of regimen to choose should be individualized based on patient characterisitics. Each class-based regimen has advantages and disadvantages that are delineated in more detail in the sections that follow and in **Tables 10–13**.

Choice of NNRTI- Versus PI-Based Initial Regimens for Children Younger Than 3 Years of Age

One special scenario is the choice of initial therapy for children < 3 years of age. The only preferred regimens for children < 3 years are coformulated lopinavir/ritonavir-based therapy and nevirapine-based therapy. Infants exposed to nevirapine in the peripertum period as part of PMTCT strategy should not be treated with nevirapine-based combination therapy because of the established higher risk of treatment failure due to nevirapine resistance *[15, 19]*, and lopinavir/ritonavir-based combination therapy would be the only recommended, preferred initial regimen. In addition, many experts in the United States recommend coformulated lopinavir/ritonavir-based therapy over nevirapine-based therapy even in the absence of peripartum nevirapine exposure because of concern about greater potential hepatotoxicity, lower barrier to resistance, and higher rate of virologic failure with nevirapine compared with lopinavir/ritonavir *[20-22]*. However, evidence is lacking for increased toxicity of nevirapine compared with lopinavir/ritonavir in infants *[15]* and some experts prefer nevirapine-based therapy because of the poor palatability of liquid lopinavir/ritonavir. Ongoing studies are expected to provide clearer evidence about the relative superiority of NNRTI- versus PI-based regimens in infants and children.

PREFERRED REGIMENS FOR INITIAL THERAPY OF CHILDREN (TABLE 8)

NNRTI-Based Regimens (one NNRTI + two-NRTI backbone)

Panel's Recommendations:

- ***Preferred NNRTI:***
  - ***Nevirapine in combination with two NRTIs for children age <3 years who have not been exposed to nevirapine as part of maternal-infant prophylaxis or who require a liquid formulation (BI*).***
  - ***Efavirenz in combination with two NRTIs for children age ≥3 years (AI*).***
- ***Alternative NNRTI:***
  - ***Nevirapine in combination with two NRTIs (for children age ≥3 years) (BI*).***

The Panel does not recommend the following NNRTIs as part of initial therapy in children:

- ***Etravirine is not recommended due to lack of pediatric formulation, pediatric pharmacokinetic data, efficacy or safety data in children, and lack of data in antiretroviral-naïve patients (BIII).***
- ***Nevirapine is not recommended for infants exposed to nevirapine as part of maternal-infant prophylaxis (AI).***
- ***Nevirapine is not recommended for postpubertal girls with CD4 count >250/mm^3 (AII*).***
- ***Efavirenz is not recommended for sexually active female adolescents when reliable contraception cannot be assured (BIII).***
- ***Efavirenz is not recommended for children <3 years of age (BIII).***

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an approved pediatric indication. Nevirapine is available in a liquid formulation, but efavirenz is not available in a liquid formulation in the United States. Advantages and disadvantages of different NNRTI drugs are delineated in **Table 11**. Use of NNRTIs as initial therapy preserves the PI class for future use, and less dyslipidemia and fat maldistribution have been reported with the NNRTI class than with the PI class. Additionally, there is generally a lower pill burden with these agents when compared with PI-based regimens for children taking solid formulations. The major disadvantages of the current NNRTI drugs approved for use in children arethat a single viral mutation can confer drug resistance, and cross resistance develops between nevirapine and efavirenz. In infants exposed to nevirapine as part of PMTCT, higher virologic failure rates have been demonstrated with nevirapine-based regimens compared with lopinavir/ritonavir-based regimens *[15]*. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all drugs in this class, but is most frequent with nevirapine, at least in HIV-infected adults. NNRTI drugs have the potential for drug interactions due to metabolism via hepatic enzymes; however, these are less frequent than those of boosted PI regimens.

Efavirenz, in combination with two NRTIs, is the preferred NNRTI for initial therapy of children age ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no randomized studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome and rare but potentially life-threatening hepatitis *[23-24]*, nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of antiretroviral-naïve children age ≥3 years. In infants and children <3 years who require a liquid NNRTI-based regimen, nevirapine is preferred.

Efavirenz as preferred NNRTI: In clinical trials in HIV-infected adults, a PI-sparing regimen of efavirenz in combination with zidovudine and lamivudine was associated with an excellent virologic response, with 70% of treated individuals having plasma HIV RNA <400 copies/mL at 48 weeks *[25]*. In randomized controlled trials in treatment-naïve adults, superior or similar virologic activity has been demonstrated in efavirenz-treated

patients compared with individuals receiving PI- or triple NRTI-based regimens *[26-29]*. Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below) *[30-34]*. No comparative trials have been conducted in children. However, an analysis of children and adults starting first-line antiretroviral therapy in Uganda has demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years) *[22]*.

Efavirenz has been studied in HIV-infected children in combination with two NRTIs or with an NRTI and a PI *[35-41]*. Results are comparable to those seen in adults. At this time, no pediatric formulation of efavirenz is available in the United States. The appropriate dose of efavirenz for children age <3 years has not been determined, and it is therefore not recommended for this age group. Some clinicians would recommend opening the capsules and adding the contents to food or liquid for children age ≥3 years who cannot swallow pills; however, there are no pharmacokinetic data on use in this fashion and it is not recommended.

The major limitations of efavirenz are central nervous system side effects in both children and adults; reported side effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after first initiating efavirenz. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in adult patients with higher levels of drug *[42-45]*. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults *[39, 41]*. Additionally, efavirenz is potentially teratogenic to the fetus if taken by a pregnant woman during the first trimester of pregnancy (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information). Unless adequate contraception can be ensured, it is not recommended for initial therapy in adolescent females who are sexually active and may become pregnant.

Nevirapine as alternative NNRTI: Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown antiretroviral efficacy in a number of different combination regimens (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information) *[46]*. Nevirapine has been studied in HIV-infected children in combination with two NRTIs or with an NRTI and a PI *[47-49]*.

In a large adult trial (2NN trial), although virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz), serious hepatic toxicity was more frequent in the nevirapine arm than the efavirenz arm (hepatic laboratory toxicity in 8%–14% of those on nevirapine, compared with 5% on efavirenz) *[34]*. Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens *[50]*. Additionally, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 count and in women, particularly women with CD4 >250 cells/mm^3 and men with CD4 >400 cells/mm^3. This may be less of an issue for prepubertal children. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults *[48-49, 51]*. In an FDA review of 783 HIV-infected pediatric patients, there was only 1 case of hepatitis, which was reported in a 17-year-old; there was no evidence of a serious hepatic event associated with nevirapine use in any child prior to adolescence *[51]*. In contrast, skin and hypersensitivity reactions have been reported in children *[52]*. The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown; efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported but should be attempted with caution *[53]*.

Because of the higher potential for toxicity and possibly an increased risk of virologic failure, nevirapine-based regimens are considered as alternative rather than preferred NNRTI in children age ≥3 years. Because appropriate dosing information for nevirapine in young children is available and there is a liquid formulation, nevirapine is the preferred NNRTI for children who are age <3 years or those who require a liquid formulation. Nevirapine should not be used in infants exposed to nevirapine as part of PMTCT *[15]*. Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4

count >250/mm^3 due to the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk *[24]*.

PI-Based Regimens (PIs [boosted or unboosted] + two- NRTI backbone)

Panel's Recommendations:

- ***Preferred PI:***
  - ***Lopinavir/ritonavir in combination with two NRTIs (AI*).***
- ***Alternative PI (listed alphabetically):***
  - ***Atazanavir in combination with low-dose ritonavir and two NRTIs for children age ≥6 years (AI*).***
  - ***Darunavir in combination with low-dose ritonavir and two NRTIs for children ≥6 years (AI*).***
  - ***Fosamprenavir in combination with low-dose ritonavir and two NRTIs for children age ≥6 years (AI*).***
- ***Use in special circumstances:***
  - ***Atazanavir unboosted (for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir) in combination with two NRTIs (unboosted atazanavir should not be used with tenofovir) (BII*).***
  - ***Fosamprenavir unboosted (for children age ≥2 years) in combination with two NRTIs (BIII).***
  - ***Nelfinavir in combination with two NRTIs (for children age >2 years) (BI*).***

The Panel does not recommend including the following PIs in initial therapy in children because of insufficient data, data related to toxicity or potency, or inconvenient dosing:

- ***Indinavir, saquinavir, or tipranavir (AIII).***
- ***Dual (full-dose) PIs (AIII).***
- ***Full-dose ritonavir or use of ritonavir as the sole PI (AIII).***
- ***Unboosted atazanavir in children age <13 years and/or <39 kg (AIII).***
- ***Nelfinavir in children age <2 years (AII).***
- ***Unboosted darunavir (AIII).***
- ***Once-daily dosing of lopinavir/ritonavir, boosted darunavir, or boosted or unboosted fosamprenavir (AII).***

Summary: PI-Based Regimens

Nine PIs are currently approved for use, 7 of which are approved for use in children and have pediatric drug formulations. Advantages and disadvantages of different PIs are delineated in **Table 12**. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, the drugs have potential for multiple drug interactions due to metabolism via hepatic enzymes and may be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to be considered in selecting a PI-based regimen for treatment-naïve children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), and availability of data in children (see **Table 12** for advantages and disadvantages and **Appendix B: Pediatric Antiretroviral Drug Information** for detailed pediatric information on each drug).

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs, and has been used in low doses combined with another PI as a "pharmacokinetic booster," increasing drug exposure by prolonging the second drug's half-life. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children older than 6 weeks of age *[54]* and for atazanavir, fosamprenavir, darunavir, and

tipranavir with low-dose ritonavir in children age ≥6 years. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia *[55]* and drug-drug interactions.

The Panel recommends coformulated lopinavir/ritonavir as the preferred PI for the treatment-naïve child based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information for children as young as age 6 weeks, and extensive experience as initial therapy in both resource-rich and resource-limited areas. However, data comparing the efficacy of lopinavir/ritonavir to other PIs are not available in children. Three PIs can be considered as alternative PIs for use in children age ≥6 years when used in combination with low-dose ritonavir: atazanavir, darunavir, and fosamprenavir. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir without boosting ritonavir in children age ≥2 years, atazanavir without boosting ritonavir in adolescents age ≥13 years and >39 kg, and nelfinavir in children age ≥2 years. A saquinavir/ritonavir (1,000/100 mg twice daily)-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naïve adults *[56]* and is recommended as an alternative PI for initial therapy in the guidelines for adults and adolescents *[24]*. However, saquinavir is not recommended for initial therapy in children because there is no pediatric formulation and there are limited dosing and outcome data in children. Although good virologic and immunologic responses have been observed with indinavir-based regimens in adults, there is no liquid formulation and there has been a high rate of hematuria, sterile leukocyturia, and nephrolithiasis reported in pediatric patients with this drug *[57-60]*. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults *[57, 60]*. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy. Additionally, tipranavir is not recommended for initial therapy at the present time due to limited experience in treatment-naïve children, but it may be considered for use with treatment failure.

Due to the limited data on pharmacokinetics of full-dose dual PI combination regimens in children (e.g., saquinavir plus coformulated lopinavir/ritonavir or plus nelfinavir) *[61-63]*, these combinations are not recommended as initial therapy in children, although they may have utility as components of secondary regimens for children who have failed initial therapy.

Lopinavir/ritonavir as preferred PI: In clinical trials in adults, regimens containing lopinavir/ritonavir plus 2 NRTIs have been found to have potent virologic activity in treatment-naïve patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had superior virologic efficacy to nelfinavir (plasma HIV RNA <400 copies/mL in 84% vs. 66% of patients, respectively), and drug-resistant virus in patients with detectable plasma viral load at 48 weeks was detected in none of 51 lopinavir/ritonavir-treated patients, compared with 45% of 43 nelfinavir-treated patients *[64-65]*. The rate of toxicity was similar between the groups. Lopinavir/ritonavir has been studied in both antiretroviral-naïve and -experienced children and has demonstrated durable virologic activity and low toxicity *[5, 15, 54, 66-68]*. In a study of 44 treatment-naïve children, 84% had plasma HIV RNA <400 copies/mL and 71% <50 copies/mL after 48 weeks of therapy (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information) *[68]*. In addition, dosing and efficacy data in infants as young as 6 weeks of age are available *[5, 54, 69]*. Although once-daily lopinavir/ritonavir is FDA approved for initial therapy in adults, pharmacokinetic data in children do not support a recommendation for once-daily dosing in children *[70-71]*.

Atazanavir with low-dose ritonavir as alternative PI (for children ≥6 years): Atazanavir is a once-daily PI that was approved for use in children ≥6 years of age in March 2008. It has equivalent efficacy to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naïve adults *[72-73]*. Seventy-three percent of 48 treatment-naïve South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs *[74]*. Among 41 treatment-naïve children age 6–18 in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 68% and 59% achieved viral load <400 copies/mL and <50copies/mL, respectively, by 48 weeks *[75]*. When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children ≥6 years of age *[76-77]* and in antiretroviral-naïve adults appears to be associated with fewer PI resistance mutations at virologic failure compared with atazanavir given without

ritonavir boosting *[78]*. The main adverse effect associated with atazanavir/low-dose ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher when using low-dose ritonavir boosting than atazanavir alone *[55]*.

Darunavir with low-dose ritonavir as alternative PI (for children ≥6 years): Darunavir combined with low-dose ritonavir boosting is approved for antiretroviral-naïve and -experienced adults and for children age ≥6 years. Darunavir/ritonavir (800/100 mg once daily) has been found to be noninferior to lopinavir/ritonavir (once or twice daily), both in combination with tenofovir/emtricitabine, in an adult randomized, open-label trial. Plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and in 78% of lopinavir/ritonavir recipients ($p < 0.001$). Adverse events were also less common in the darunavir/ritonavir group ($p < 0.01$) *[79]*. There are no published data about use of darunavir as part of initial treatment in children or use of once-daily darunavir in children. In a study of treatment-experienced children (6–17 years of age), twice-daily darunavir/ritonavir-based therapy was well tolerated and resulted in 48% achieving HIV-1 RNA less than 50 copies/mL, by 48 weeks *[80]*. Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from one study in treatment-experienced children and the finding of high potency and low toxicity in adults. Some experts would only recommend boosted darunavir for treatment-experienced children and reserve its use for patients with PI resistant mutations. Once-daily dosing of darunavir is not recommended for children.

Fosamprenavir with low-dose ritonavir as alternative PI (for children ≥6 years): Fosamprenavir (the prodrug of amprenavir) is now available in a pediatric liquid formulation and a tablet formulation. Amprenavir is no longer manufactured. In June 2007, fosamprenavir suspension was approved for use in pediatric patients ≥2 years of age. The approval was based on two open-label studies in pediatric patients between 2 and 18 years of age *[81-82]*. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information). There is less pediatric experience with fosamprenavir than with lopinavir/ritonavir. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to lopinavir/ritonavir r *[83]*. In children age ≥6 years, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. Data on appropriate dosing of fosamprenavir in combination with low-dose ritonavir in children age <6 years are not available; therefore, this combination cannot be recommended in that age group. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

PIs for use in special circumstances

Atazanavir without ritonavir boosting in children age ≥13 years: Although unboosted atazanavir is approved for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir, data from the ongoing IMPAACT/PACTG 1020A study indicate that higher doses (on a mg/m^2 basis) are required to achieve adequate drug concentrations (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naïve patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because of inferior virologic response demonstrated for this combination in adults in ACTG 5175 *[84]*. If these agents are to be used in combination, patients should be instructed to take them at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach.

Fosamprenavir without ritonavir boosting in children age ≥2 years: Fosamprenavir without ritonavir boosting has been studied in children age ≥2 years but is only recommended in special circumstances when preferred or alternative PI-based regimens cannot be used.

Nelfinavir for children ≥2 year): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children age ≥2 years in special circumstances. There is extensive pediatric experience with nelfinavir-based regimens in antiretroviral-naïve and -experienced children, with follow-up in children receiving the regimen for as long as 7 years *[85]*. The drug has been well tolerated, with diarrhea as the primary side effect, but virologic potency has been highly variable between studies, with reported rates of virologic suppression ranging 26%–69% (see **Appendix B: Pediatric Antiretroviral Drug Information** for

detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naïve pediatric patients *[86]*. In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% in children with therapeutic nelfinavir troughs (>0.8 mg/L) *[86]*. There is large interpatient variability in plasma concentrations in children, with lower levels in younger children *[87-92]*. The optimal dose of nelfinavir in younger children, particularly those age <2 years, has not been well defined, and higher doses of nelfinavir (relative to body size) are required to achieve adequate drug levels in infants than in older children *[87]*. Pharmacokinetic parameters in adolescent patients have not been well studied, and doses higher than those recommended in adults may be required for some patients. These data, combined with data in adults showing lesser potency of nelfinavir compared with other protease inhibitors and efavirenz, balanced against the advantage of a protease inhibitor that is not coadminstered with low-dose ritonavir for boosting *[65, 93-96]*, make nelfinavir an agent for use in special circumstances in treatment-naïve children age ≥2 years and not recommended for treatment of children age <2 years.

The pediatric powder formulation of nelfinavir has a poor acceptance rate when mixed with food or formula, and the pharmacokinetics of the drug is extremely variable in children. To overcome the problems associated with this formulation, tablets are dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable pharmacokinetic parameters in a study in adults *[97]*.

Triple-NRTI Regimens

Panel's Recommendations:

- ***Preferred: None***
- ***Alternative: None***
- ***Use in special circumstances:***
  - ***A three-NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or adherence concerns) (BI*).***

The Panel does not recommend any other triple-NRTI regimens as initial therapy in children due to inferior virologic potency or lack of comparative data (AIII).

Summary: Triple-NRTI Regimens

Triple-NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Data on the efficacy of triple-NRTI regimens for treatment of antiretroviral-naïve children are limited; in small observational studies, response rates of 47%–50% have been reported *[98-99]*. In adult trials, these regimens have shown less potent virologic activity when compared with NNRTI- or PI-based regimens. Based on the results of these clinical trials, the Panel recommends that a three-NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or concerns related to adherence).

Following is a discussion of findings in clinical trials of triple-NRTI regimens:

Zidovudine + lamivudine + abacavir: In a randomized trial, the triple-NRTI combination of zidovudine + lamivudine + abacavir was shown to reduce viral load to <400 copies/mL in 51% of treatment-naïve adults at 48 weeks of therapy, results equivalent to those of the PI-based comparison arm of zidovudine + lamivudine + indinavir *[100]*. In a study of this regimen in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining a viral load of <400 copies/mL at

48 weeks of treatment *[101]*. Additionally, a clinical trial (ACTG 5095) in antiretroviral-naïve adults that compared initial therapy with abacavir + zidovudine + lamivudine to efavirenz + zidovudine + lamivudine or efavirenz + abacavir + zidovudine + lamivudine found that the triple-NRTI regimen was inferior to the efavirenz-based regimens, with a higher incidence of and an earlier time to virologic failure; after 48 weeks of therapy, 74% of adults receiving the triple-NRTI regimen had HIV RNA <200 copies/mL, compared with 89% of patients receiving efavirenz-based regimens *[26, 102]*.

Other triple-NRTI regimens: Clinical trials in adults also have investigated triple-NRTI regimens consisting of stavudine + didanosine + lamivudine, stavudine + lamivudine + abacavir, and didanosine + stavudine + abacavir *[103-104]*. The virologic response to all these regimens was inferior to viral suppression achieved in comparator regimens. In addition, the M184V lamivudine drug-resistance mutation was seen more frequently in patients treated with triple-NRTI regimens containing lamivudine. Triple-NRTI regimens containing tenofovir have been studied in adults. Tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine demonstrate significantly increased rates of virologic failure and are not recommended *[105-107]*. Tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults but no comparative data are available and the regimen is not recommended *[108]*.

Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy

Panel's Recommendations (listed alphabetically):

- ***Preferred two-NRTI backbone combinations:***
  - ***Abacavir + (lamivudine or emtricitabine) (AI).***
    - ***HLA-B*5701 genetic testing should be performed prior to initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 (AII*).***
  - ***Didanosine + (lamivudine or emtricitabine) (BI*).***
  - ***Zidovudine + (lamivudine or emtricitabine) (AI*).***
  - ***For postpubertal or Tanner stage 4 adolescents only: tenofovir + (lamivudine or emtricitabine) (A-I*).***
- ***Alternative two-NRTI backbone combinations:***
  - ***Zidovudine + (abacavir or didanosine) (BII).***
- ***Use in special circumstances:***
  - ***Stavudine + (lamivudine or emtricitabine) (BII).***

The Panel does not recommend the following dual-NRTI backbones for initial therapy in children:

- ***Stavudine + didanosine due to increased toxicity (AII).***
- ***Abacavir + didanosine, abacavir + tenofovir, and didanosine + tenofovir due to insufficient data (BIII).***
- ***Tenofovir as part of any dual-NRTI backbone in children in Tanner stages 1–3 due to lack of pediatric dosing data and formulation and concerns related to bone toxicity (BII).***

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, six NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA approved for use in children younger than 13 years of age. Dual-NRTI combinations form the "backbone" of combination regimens for both adults and children. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; and emtricitabine in combination with stavudine or didanosine *[6, 37, 85, 91, 109-110]*. Advantages and disadvantages of different dual-NRTI backbone options are delineated in **Table 10**.

The preferred dual-NRTI combinations for initial therapy in children consist of abacavir, didanosine, or zidovudine combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine. This combination has extensive data on safety in children and is generally well tolerated. The major toxicities are bone marrow suppression, manifested as macrocytic anemia and neutropenia. Minor toxicities include gastrointestinal toxicity and fatigue. The combination of zidovudine and didanosine had the lowest rate of toxicities in a large retrospective study of children *[111]*.

Both lamivudine and emtricitabine are well tolerated with few side effects. Although there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir, didanosine, or zidovudine). The advantages of emtricitabine are once-daily administration, ability to be coadministered with didanosine as a once-daily NRTI backbone option, and availability as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine; and improved susceptibility to zidovudine, stavudine, and tenofovir *[112-113]*.

Abacavir in combination with lamivudine has been shown to be as potent or possibly more potent than zidovudine in combination with lamivudine in both children and adults *[114-115]* but has the potential for abacavir-associated life-threatening hypersensitivity reactions in a small proportion of patients. In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir *[115]*. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see **Appendix B: Pediatric Antiretroviral Drug Information**); however the prevalence of HLA-B*5701 is much lower in African American and Hispanic than white individuals in the United States (2%–2.5% compared with 8%) *[116]*. Pretreatment screening for HLA-B*5701 prior to initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir hypersensitivity reaction in HIV-infected adults (from 7.8% to 3.4%) *[117]*. Genetic screening for HLA-B*5701 should be performed for HIV-infected children prior to initiating abacavir-based therapy and abacavir should not be given to those who test positive for HLA-B*5701.

Didanosine in combination with lamivudine or emtricitabine are also preferred dual-NRTI combinations. The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naïve children age 3 to 21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy *[37]*. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who feed frequently and may decrease medication compliance in older children by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food *[118]*. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation *[119-122]*. Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents in Tanner stage 4 or who are postpuberty. The fixed-dose combinations of tenofovir + emtricitabine and tenofovir + emtricitabine + efavirenz are both administered as 1 pill once daily and may be particularly useful to improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine/efavirenz in viral efficacy *[123-124]*. In ACTG 5202, adults were randomly assigned to tenofovir + emtricitabine versus abacavir + lamivudine in combination with boosted atazanavir versus efavirenz (in factorial design). Among those with screening HIV-1 RNA ≥100,000 copies per mL, the times to virologic failure and to first adverse event were both significantly shorter in patients randomly assigned to abacavir + lamivudine than in those assigned to tenofovir + emtricitabine. Results for patients with lower entry viral loads and for comparisons by assignment to efavirenz or boosted atazanavir are not yet available *[125]*. In other nonrandomized studies, 48-week virologic efficacy of tenofovir + emtricitabine in combination with

lopinavir/ritonavir was similar to that seen in trials with other dual-NRTI backbones in treatment-naïve adults *[126]*. However, decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks in some, although not all, studies *[119-122, 127]*. At this time data are insufficient to recommend use of this drug for initial therapy in infected children in Tanner stages 1–3, in whom the risk of bone toxicity may be greatest *[119, 122]* (see **Appendix B: Pediatric Antiretroviral Drug Information** for more detailed pediatric information). Renal toxicity has been reported in children as well as adults receiving tenofovir; in 1 single-center study, the rate of beta-2-microglobulinuria was higher in children receiving tenofovir than children receiving other antiretroviral agents (12/44 compared with 2/48, respectively), although creatinine clearance did not differ between groups *[128]*. Because of potential bone toxicity and renal toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment-naïve children. There are numerous drug-drug interactions with tenofovir and other antiretroviral drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, that complicate appropriate dosing of this drug.

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine. There is considerable experience with use of these dual-NRTI regimens in children *[111]*. However, both zidovudine + abacavir and zidovudine + lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir + lamivudine in one European pediatric study *[91, 115]*.

The dual-NRTI combination of stavudine with lamivudine or emtricitabine is recommended for use only in special circumstances because stavudine is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs *[129-131]*. Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than those receiving zidovudine-containing combinations *[111]*. In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferred to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

Certain dual-NRTI drug combinations are not recommended. These include zidovudine + stavudine due to pharmacologic interactions that can result in potential virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the same single resistance mutation confers cross resistance, so these drugs should not be used in combination. The dual-NRTI combination of stavudine + didanosine is also not recommended for use as initial therapy. In small pediatric studies, stavudine + didanosine demonstrated virologic efficacy and was well tolerated *[109-110, 132]*. However, in studies in adults, stavudine + didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine + lamivudine *[133-134]*; additionally, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy *[129, 135]*. Abacavir + didanosine, abacavir + tenofovir, and didanosine + tenofovir are not recommended as dual-NRTI backbones in initial therapy on the basis of insufficient data in children.

***Not* Recommended for *Initial* Therapy for Children Because of Insufficient Data**

Panel's Recommendations:

Because of insufficient data for use as initial therapy, the following regimens (in addition to those already discussed in previous sections) should not be offered to children for initial therapy (AIII):

- ***Triple-class regimens, including NRTI plus NNRTI plus PI***
- ***Maraviroc-containing regimens***
- ***Raltegravir-containing regimens***
- ***Enfuvirtide (T-20)-containing regimens***

A number of antiretroviral drugs and drug regimens are not recommended for initial therapy of antiretroviral-naïve children because of insufficient pediatric data. These are summarized below.

Regimens containing three drug classes: Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naïve children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options *[38-40]*.

New agents without sufficient pediatric data for use as initial therapy (Tables 13 and 14): At this time several new agents appear promising in adults but do not have sufficient pediatric pharmacokinetic and safety data to recommend their use as components of an initial therapeutic regimen in children. These include maraviroc (a CCR5 antagonist), raltegravir (an integrase inhibitor), tenofovir (in children Tanner stages 1–3), and etravirine (a new NNRTI). Raltegravir is being evaluated in treatment-experienced children, but pharmacokinetic, safety, and efficacy data are not yet available and no pediatric formulation is commercially available. Tipranavir boosted with ritonavir was approved (June 2008) by the FDA for use in treatment-experienced children age 2–18 years, but data are insufficient to address use as initial therapy.

Enfuvirtide (T-20), a fusion inhibitor, is approved for use in children age ≥6 years in combination with other antiretroviral drugs in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. The drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Data are currently insufficient to recommend use of enfuvirtide for initial therapy of children.

Antiretroviral Drug Regimens that Should Never be Offered (Table 9)

Panel's Recommendations:

The following regimens or regimen components should never be offered to HIV-infected children:

- ***Monotherapy (AII)***
- ***Two NRTIs alone (AI)***
- ***Certain two-NRTI combinations as part of a combination regimen:***
  - ***Lamivudine + emtricitabine due to similar resistance pattern and no additive benefit (AIII)***
  - ***Zidovudine + stavudine due to virologic antagonism (AII)***
- ***Dual-NNRTI combinations (AI*)***
- ***Unboosted saquinavir, darunavir, or tipranavir (AII*)***
- ***Atazanavir + indinavir (AIII)***
- ***Certain NRTI-only regimens***
  - ***Tenofovir + didanosine + (lamivudine or emtricitabine) (AI*)***
  - ***Tenofovir + abacavir + (lamivudine or emtricitabine) (AI*)***

Several antiretroviral drugs and drug regimens are not recommended for use in therapy of children or adults. These are summarized below. Clinicians should be aware of the components of fixed-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Monotherapy: Therapy with a single antiretroviral drug is not recommended because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drug being used and cross resistance to other drugs within the same drug class. The exception is for prophylaxis for the newborn infant born to an HIV-infected mother, in which case 6 weeks of monotherapy with zidovudine is recommended for the infant (unless the infant is identified as HIV infected, in which case zidovudine should be discontinued and standard triple therapy instituted) *[24]*.

Dual-nucleoside regimens alone: Dual-NRTI therapy alone is not recommended for initial therapy because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drugs being used and cross resistance to other drugs within the same drug class. For children previously initiated on a

dual-NRTI regimen who have achieved viral suppression, it is reasonable to either continue on this therapy or to add a PI or NNRTI to the regimen. If a child is to stay on a two-NRTI regimen, the plan should be to change to a three or more drug combination if viral rebound should occur (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

In special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence, there may be a role for use of single- or dual-NRTI regimens as holding or bridging regimens, while intensively working on improving adherence in preparation for initiation of a new, suppressive combination antiretroviral regimen (see section on **Approach to the Management of Antiretroviral Treatment Failure**).

Certain dual-nucleoside backbone combinations: Certain dual-NRTI combinations (zidovudine + stavudine, emtricitabine + lamivudine) are not recommended for therapy at any time because of pharmacological antagonism or inferior virologic response. Emtricitabine should not be used in combination with lamivudine because the drug structure is similar and the same single resistance mutation (M184V) induces resistance to both drugs.

Dual non-nucleoside reverse transcriptase inhibitors (NNRTIs): An adult study (2NN) demonstrated increased toxicity with the combination of nevirapine plus efavirenz *[34]*.

Certain PIs: The combination of atazanavir + indinavir has the potential for additive hyperbilirubinemia. Unboosted saquinavir, darunavir, and tipranivir have low bioavailablity and do not achieve adequate drug levels, and therefore should not be used without ritonavir boosting.

Three-NRTI regimen of tenofovir + (didanosine or abacavir) + (lamivudine or emtricitabine): The triple-NRTI combinations of tenofovir with (didanosine or abacavir) plus (lamivudine or emtricitabine) have a high rate of early virologic nonresponse when used as initial therapy in treatment-naïve adults and are not recommended as combination therapy for children at any time *[105-107]*.

Table 8. Antiretroviral Regimens Recommended for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children

A combination antiretroviral regimen in treatment-naïve children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. A 3-NRTI regimen consisting of zidovudine, abacavir, and lamivudine is recommended only if a PI or NNRTI regimen cannot be used. Regimens should be individualized based on advantages and disadvantages of each combination (see **Tables 11–13**).

Preferred Regimens	
Children <3 years of age:	Two NRTIs ***plus*** lopinavir/ritonavir[3]
	Two NRTIs ***plus*** nevirapine[1,3] (only if no peripartum nevirapine exposure)
Children ≥3 years of age:	Two NRTIs ***plus*** lopinavir/ritonavir[3]
	Two NRTIs ***plus*** efavirenz[1]
Alternative Regimens	
Children <3 years of age:	None
Children ≥3 to <6 years of age:	Two NRTIs ***plus*** nevirapine[1,3]
Children ≥6 years of age	Two NRTIs ***plus*** atazanavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** darunavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** fosamprenavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** nevirapine[1,3]
Use in Special Circumstances	
	Two NRTIs ***plus*** atazanavir unboosted (for treatment-naïve adolescents ≥13 years of age and >39 kg)
	Two NRTIs ***plus*** fosamprenavir unboosted (children ≥2 years of age)
	Two NRTIs ***plus*** nelfinavir (children ≥2 years of age)
	Zidovudine ***plus*** lamivudine ***plus*** abacavir
2-NRTI Backbone Options (for use in combination with additional drugs) (alphabetical ordering)	
Preferred	Abacavir ***plus*** (lamivudine ***or*** emtricitabine)
	Didanosine ***plus*** (lamivudine ***or*** emtricitabine)
	Tenofovir ***plus*** (lamivudine ***or*** emtricitabine) (for Tanner stage 4 or postpubertal adolescents only)
	Zidovudine ***plus*** (lamivudine ***or*** emtricitabine)
Alternative	Zidovudine ***plus*** abacavir
	Zidovudine ***plus*** didanosine
Use in Special Circumstances	Stavudine ***plus*** (lamivudine ***or*** emtricitabine)

Not Recommended for Initial Therapy
Etravirine-containing regimens
Efavirenz-containing regimens for children <3 years of age
Tipranavir-containing regimens
Saquinavir-containing regimens
Indinavir-containing regimens
Dual (full-dose) PI regimens
Full-dose ritonavir or use of ritonavir as the sole PI
Unboosted atazanavir-containing regimens in children <13 years of age and/or <39 kg
Nelfinavir-containing regimens for children <2 years old
Unboosted darunavir regimens using once-daily dosing of lopinavir/ritonavir, boosted darunavir, or fosamprenavir (boosted or unboosted)
Triple-NRTI regimens other than abacavir + zidovudine + lamivudine
Triple-class regimens, including NRTI *plus* NNRTI *plus* PI
Regimens with dual-NRTI backbones of abacavir + didanosine, abacavir + tenofovir, didanosine + tenofovir , and didanosine + stavudine
Tenofovir-containing regimens in children in Tanner stages 1–3
Maraviroc-containing regimens
Raltegravir-containing regimens
Enfuvirtide (T-20)-containing regimens

[1] Efavirenz is currently available only in capsule form and should be used only in children ≥3 years of age with weight ≥10 kg; nevirapine would be the preferred NNRTI for children age <3 years of age (excluding infants who were exposed to nevirapine as part of maternal-infant peripartum prophylaxis) or who require a liquid formulation. Unless adequate contraception can be ensured, efavirenz-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[2] With the exception of lopinavir/ritonavir at all ages and atazanavir/ritonavir, fosamprenavir/ritonavir, and darunavir/ritonavir in children ≥6 years of age, use of other boosted PIs as a component of initial therapy is not recommended, although such regimens have utility as secondary treatment regimens for children who have failed initial therapy.

[3] For children <3 years of age, nevirapine is the preferred NNRTI when NNRTI-based therapy is used. However, lopinavir/ritonavir is preferred to nevirapine by many experts. Nevirapine should not be used in infants who have been exposed to nevirapine as part of maternal-infant prophylaxis.

[4] Nevirapine should not be used in postpubertal girls with CD4 count >250/mm^3, unless the benefit clearly outweighs the risk.

Table 9. Antiretroviral Regimens or Components that Should Never Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children

	Rationale	Exceptions
Antiretroviral regimens never recommended for children		
Monotherapy	• Rapid development of resistance • Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs	• Not recommended for initial therapy; for patients currently on this treatment, some clinicians may opt to continue if virologic goals are achieved
Tenofovir ***plus*** abacavir ***plus*** lamivudine ***or*** emtricitabine as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults	• No exception
Tenofovir ***plus*** didanosine ***plus*** lamivudine ***or*** emtricitabine as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults	• No exception
Antiretroviral components never recommended as part of an antiretroviral regimen for children		
Atazanavir ***plus*** indinavir	• Potential additive hyperbilirubinemia	• No exception
Dual-NNRTI combinations	• Enhanced toxicity	• No exception
Dual-NRTI combinations:		
• Lamivudine ***plus*** emtricitabine	• Similar resistance profile and no additive benefit	• No exception
• Stavudine ***plus*** zidovudine	• Antagonistic effect on HIV	• No exception
Efavirenz in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other antiretroviral option is available and potential benefits outweigh risks
Nevirapine initiation in adolescent girls with CD4 >250 cells/mm^3 or adolescent boys with CD4 >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs the risk
Unboosted saquinavir, darunavir, or tipranavir	• Poor oral bioavailablity • Inferior virologic activity compared with other protease inhibitors	• No exception

Table 10. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
Preferred Combinations		
Abacavir ***plus*** lamivudine ***or*** emtricitabine	• Palatable liquid formulations • Can give with food • Abacavir and lamivudine are coformulated as a single pill for older/larger patients	• Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment
Didanosine ***plus*** lamivudine ***or*** emtricitabine	• Delayed-release capsules of didanosine may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily emtricitabine • Emtricitabine available as a palatable liquid formulation administered once daily	• Food effect (didanosine is recommended to be taken 1 hour before or 2 hours after food) – some experts give didanosine without regard to food in infants or when compliance is an issue (but can be coadministered with emtricitabine or lamivudine) • Limited pediatric experience using delayed-release didanosine capsules in younger children • Pancreatitis, neurotoxicity with didanosine
Zidovudine ***plus*** lamivudine ***or*** emtricitabine	• Extensive pediatric experience • Zidovudine and lamivudine are coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • Emtricitabine available as a palatable liquid formulation administered once daily	• Bone marrow suppression with zidovudine • Lipoatrophy with zidovudine
Tenofovir ***plus*** lamivudine ***or*** emtricitabine for Tanner stage 4 or postpubertal adolescents only	• Resistance slow to develop • Once-daily dosing for tenofovir • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children • Tenofovir and emtricitabine are coformulated as single pill for older/larger patients	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing
Alternate Combinations		
Zidovudine ***plus*** abacavir	• Palatable liquid formulations • Can give with food	• Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment • Bone marrow suppression and lipoatrophy with zidovudine
Zidovudine ***plus*** didanosine	• Extensive pediatric experience • Delayed-release capsules of didanosine may allow once-daily dosing of didanosine in older children able to swallow pills and who can receive adult dosing	• Bone marrow suppression and lipoatrophy with zidovudine • Pancreatitis, neurotoxicity with didanosine • Didanosine liquid formulation less palatable than lamivudine or emtricitabine liquid formulation • Food effect (recommended to take didanosine 1 hour before or 2 hours after food); some experts give didanosine without regard to food in infants or when compliance is an issue

	Advantages	Disadvantages
Use in Special Circumstances		
Stavudine ***plus*** lamivudine ***or*** emtricitabine	• Moderate pediatric experience • Palatable liquid formulations • Can give with food • Emtricitabine available as a palatable liquid formulation administered once daily	• Stavudine associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Limited pediatric experience with stavudine plus emtricitabine
Not Recommended		
Tenofovir-containing regimens in children in Tanner stages 1–3	• Resistance slow to develop • Once-daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food	• No pediatric formulation of tenofovir • Limited PK data for tenofovir in children • Limited pediatric experience • Potential bone and renal toxicity; bone toxicity appears to be more frequent in younger children • Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing
Zidovudine ***plus*** stavudine	• None	• Pharmacologic and antiviral antagonism
Lamivudine ***plus*** emtricitabine	• None	• Similar drug structure • Single mutation (M184V) associated with resistance to both drugs
Stavudine ***plus*** Didanosine	• Has shown antiviral activity in small studies in children • Although not recommended for initial therapy, it may be considered for use in antiretroviral-experienced children who require a change in therapy	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis

Table 11. Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
General Issues		
NNRTI-Based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than protease inhibitors • Protease inhibitor sparing • Lower pill burden than protease inhibitors for those taking solid formulation; easier to use and adhere to than protease inhibitor-based regimens	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross resistance between efavirenz and nevirapine • Rare but serious and potentially life-threatening cases of skin rash, including Stevens-Johnson syndrome, and hepatic toxicity with all NNRTIs (but highest with nevirapine) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
Preferred		
Efavirenz (for children ≥3 years of age and who can take capsules)	• Potent antiretroviral activity • Once-daily administration • Can give with food (but avoid high fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children age <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age
Nevirapine for children age <3 years who have not been exposed to nevirapine as part of maternal-infant prophylaxis or who require a liquid formulation	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence of rash/hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Decreased virologic response compared with efavirenz • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of nevirapine metabolism and is associated with a lower incidence of toxicity.
Alternative		
Nevirapine (for children age ≥3 years)	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence of rash/hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Decreased virologic response compared with efavirenz • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of nevirapine metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing

	Advantages	Disadvantages
Not Recommended		
Efavirenz (for children age <3 years)	• Potent antiretroviral activity • Once-daily administration • Can give with food (but avoid high fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children age <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age
Etravirine	• Three or more baseline NNRTI mutations result in a decreased virologic response • Patients with a history of NNRTI-related rash do not appear to be at increased risk of etravirine-related rash	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naïve patients • Multiple drug interactions with PIs and other medications • Twice-daily dosing • Skin rash

Table 12. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
General Issues		
Protease Inhibitor-Based Regimens	**Protease Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to protease inhibitors requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**Protease Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for those taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
Lopinavir/ritonavir	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with food or snack	• Poor palatability of liquid (bitter taste), although better than ritonavir alone • Food effect (liquid should be administered with food) • Ritonavir component associated with large number of drug interactions (see ritonavir) • Use with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of electrocardiogram)
Alternative		
Atazanavir in combination with low-dose ritonavir in children age ≥6 years	• Once-daily dosing • Atazanavir has less effect on triglyceride and total cholesterol levels than other PIs (but ritonavir boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)
Fosamprenavir in combination with low-dose ritonavir in children age ≥6 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • Ritonavir component associated with large number of drug interactions (see ritonavir) • Contains sulfa moiety; potential for cross sensitivity between fosamprenavir and other drugs in sulfonamide class is unknown.
Darunavir in combination with low-dose ritonavir in children age ≥6 years	• Effective in PI-experienced children when given with low-dose ritonavir boosting	• Pediatric data limited to antiretroviral-experienced children • Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations • Contains sulfa moiety; potential for cross sensitivity between darunavir and other drugs in sulfonamide class is unknown.

	Advantages	Disadvantages
Use in Special Circumstances		
Fosamprenavir (unboosted) in children age ≥2 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • May require boosted regimen to achieve adequate plasma concentrations but pharmacokinetic data to define appropriate dosing not yet available
Atazanavir (unboosted) in treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir	• Once-daily dosing • Less effect on triglyceride and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations • Unboosted atazanavir cannot be used with tenofovir
Nelfinavir in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3 times daily dosing for younger children • Adolescents may require higher doses than adults • Less potent that boosted PIs
Not Recommended		
Atazanavir (unboosted) in children <13 years of age and/or <39 kg	• Once-daily dosing (>13 years) • Less effect on triglyceride and total cholesterol levels than other PIs	• Drug levels low if used without ritonavir boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Indinavir (unboosted or boosted)	• May be considered for use as component of a regimen in combination with low-dose ritonavir in postpubertal adolescents who weigh enough to receive adult dosing	• Only available in capsule • Possible higher incidence of nephrotoxicity in children • Requires 3 times daily dosing unless boosted with ritonavir • High fluid intake required to prevent nephrolithiasis • Food effect (should be taken 1 hour before or 2 hours after food) • Limited pediatric pharmacokinetic data
Tipranavir	• Effective in PI-experienced children and adults when given with low-dose ritonavir boosting • Liquid formulation	• Limited data in treatment-naïve patients • Food effect (should be administered with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations
Ritonavir (full dose)	• Liquid formulation • Can be given with food	• Poor palatability of liquid (bitter taste) • Gastrointestinal intolerance • Food effect (should be administered with food) • Largest number drug interactions (most potent inhibitor of CYP3A4)

Table 12: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children
Page 3 of 3

	Advantages	Disadvantages
Not Recommended (continued)		
Nelfinavir in children age <2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3 times daily dosing for younger children • Adolescents may require higher doses than adults • Less potent that boosted PIs
Saquinavir (unboosted or boosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric pharmacokinetic data; will require boosting with another PI (e.g., ritonavir) to achieve adequate concentrations • No liquid formulation • High pill burden • Must be taken with food • Photosensitivity reactions can occur

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with enfuvirtide • CCR5 inhibitors ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus
Use in Special Circumstances		
Enfuvirtide	• Susceptibility of HIV to a new class of ARVs • Route of administration ensures adequate drug levels	• Twice-daily subcutaneous injections • 98%–100% incidence of local injection site reactions • Poor adherence and limited levels of success in adolescents due to local site reactions
Insufficient Data to Recommend		
Maraviroc	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual-tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation • Multiple drug interactions; different dosing depending on which NNRTI or PI is coadministered

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety
Insufficient Data to Recommend		
Raltegravir	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Limited data on pediatric dosing or safety • No pediatric formulation • Rare systemic allergic reaction or hepatitis

References

1. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
2. Chiappini E, Galli L, Gabiano C, et al. Early triple therapy vs mono or dual therapy for children with perinatal HIV infection. *JAMA.* 2006;295(6):626-628.
3. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA.* 2000;284(2):190-197.
4. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med.* 2001;345(21):1522-1528.
5. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
6. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
7. Cane P, Chrystie I, Dunn D, et al. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ.* 2005;331(7529):1368.
8. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
9. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis.* 2006;194(11):1505-1509.
10. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
11. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
12. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
13. Parker MM, Wade N, Lloyd RM, Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr.* 2003;32(3):292-297.
14. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
15. Palumbo P, Violari A, Lindsey J, et al. Nevirapine (NVP) vs lopinavir-ritonavir (LPV/r)-based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV-infected infants: preliminary results from the IMPAACT P1060 trial. Paper presented at: 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPEB12.
16. Fiscus SA, Kovacs A, Petch LA, et al. Baseline resistance to nucleoside reverse transcriptase inhibitors fails to predict virologic response to combination therapy in children (PACTG 338). *AIDS Res Ther.* 2007;4:2.
17. Hecht FM, Grant RM. Resistance testing in drug-naive HIV-infected patients: is it time? *Clin Infect Dis.* 2005;41(9):1324-1325.
18. MacLeod IJ, Rowley CF, Thior I, et al. Minor resistant variants in nevirapine-exposed infants may predict virologic failure on nevirapine-containing ART. *J Clin Virol.* 2010;48(3):162-167.
19. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
20. Jaspan HB, Berrisford AE, Boulle AM. Two-year outcomes of children on non-nucleoside reverse transcriptase inhibitor and protease inhibitor regimens in a South African pediatric antiretroviral program. *Pediatr Infect Dis J.* 2008;27(11):993-998.
21. Muller AD, Myer L, Jaspan H. Virological suppression achieved with suboptimal adherence levels among South African children receiving boosted protease inhibitor-based antiretroviral therapy. *Clin Infect Dis.* 2009;48(1):e3-5.
22. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;46(2):187-193.

23. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.
24. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
25. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
26. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350(18):1850-1861.
27. Lucas GM, Chaisson RE, Moore RD. Comparison of initial combination antiretroviral therapy with a single protease inhibitor, ritonavir and saquinavir, or efavirenz. *AIDS.* 2001;15(13):1679-1686.
28. Pulido F, Arribas JR, Miro JM, et al. Clinical, virologic, and immunologic response to efavirenz-or protease inhibitor-based highly active antiretroviral therapy in a cohort of antiretroviral-naive patients with advanced HIV infection (EfaVIP 2 study). *J Acquir Immune Defic Syndr.* 2004;35(4):343-350.
29. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER Cohort. *J Antimicrob Chemother.* 2005;56(1):190-195.
30. Carr A. Antiretroviral therapy for previously untreated HIV-1-infected adults: 2NN, or just one? *Lancet.* 2004;363(9417):1248-1250.
31. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. *J Infect Dis.* 2002;185(8):1062-1069.
32. Manfredi R, Calza L, Chiodo F. Efavirenz versus nevirapine in current clinical practice: a prospective, open-label observational study. *J Acquir Immune Defic Syndr.* 2004;35(5):492-502.
33. Manosuthi W, Sungkanuparph S, Vibhagool A, et al. Nevirapine- versus efavirenz-based highly active antiretroviral therapy regimens in antiretroviral-naive patients with advanced HIV infection. *HIV Med.* 2004;5(2):105-109.
34. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* 2004;363(9417):1253-1263.
35. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
36. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res.* 2005;10(12):503-508.
37. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
38. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis.* 2000;182(6):1769-1773.
39. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
40. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
41. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS.* 2001;15(2):241-243.
42. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648-1653.
43. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS.* 2001;15(1):71-75.
44. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS.* 2002;16(9):1201-1215.
45. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care.* 2006;4(1).
46. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs.* 2000;2(5):373-407.
47. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.

48. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
49. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS.* 2003;17(11):1639-1647.
50. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology.* 2002;35(1):182-189.
51. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, MA. Abstract 776.
52. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.
53. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis.* 2007;7(11):733-738.
54. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.
55. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis.* 2007;44(11):1484-1492.
56. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr.* 2009;50(4):367-374.
57. Fraaij PL, Verweel G, van Rossum AM, et al. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection.* 2007;35(3):186-189.
58. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
59. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
60. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics.* 2002;110(2 Pt 1):e19.
61. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
62. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
63. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
64. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis.* 2004;189(1):51-60.
65. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
66. De Luca M, Miccinesi G, Chiappini E, et al. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol.* 2005;18(4):729-735.
67. Havens P, Frank M, Cuene B, et al. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m2/dose in children and adolescents with HIV infection. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 937.
68. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2003;22(3):216-224.

69. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
70. la Porte C, van Heeswijk R, Mitchell CD, et al. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther.* 2009;14(4):603-606.
71. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther.* 2008;13(8):1087-1090.
72. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004;36(5):1011-1019.
73. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet.* 2008;372(9639):646-655.
74. Meyers T, Rutstein R, Samson P, et al. Treatment responses to atazanavir-containing HAART in a drug-naïve paediatric population in South Africa. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Abstract 582.
75. Bristol-Myers Squibb. Reyataz Package Insert. 2010; http://packageinserts.bms.com/pi/pi_reyataz.pdf.
76. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2008;52(2):631-637.
77. Kiser J, Rutstein R, Aldrovandi G, et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25 2005; Boston, MA. Abstract 767.
78. Stebbing J, Nathan B, Jones R, et al. Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS.* 2007;21(13):1826-1828.
79. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS.* 2008;22(12):1389-1397.
80. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS.* 2009;23(15):2005-2013.
81. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 719.
82. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 718.
83. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* 2006;368(9534):476-482.
84. National Institute of Allergy and Infectious Diseases (NIAID). Bulletin monitoring board recommends stopping experimental treatment regimen in international study of patients new to HIV treatment. 2008; http://www.niaid.nih.gov/news/newsreleases/2008/Pages/ACTG_5175.aspx.
85. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
86. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr.* 2004;145(3):403-405.
87. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J.* 2001;20(8):746-751.
88. Floren LC, Wiznia A, Hayashi S, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics.* 2003;112(3 Pt 1):e220-227.
89. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother.* 2006;50(3):910-916.
90. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 2003;22(1):48-55.

91. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
92. van Heeswijk RP, Scherpbier HJ, de Koning LA, et al. The pharmacokinetics of nelfinavir in HIV-1-infected children. *Ther Drug Monit.* 2002;24(4):487-491.
93. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2004;35(1):22-32.
94. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.* 2004;18(11):1529-1537.
95. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
96. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis.* 2006;6:107.
97. Regazzi MB, Seminari E, Villani P, et al. Nelfinavir suspension obtained from nelfinavir tablets has equivalent pharmacokinetic profile. *J Chemother.* 2001;13(5):569-574.
98. Saavedra J, Mccoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Paper presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; September 22-25, 2001; Chicago, IL. Abstract 1941.
99. Wells C, Sharland M, Smith C, et al. Triple nucleoside analogue therapy with zidovudine (AZT), lamivudine (3TC), and abacavir (ABC) in the paediatric HIV London south network (phils-net) cohort. Paper presented at: XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Abstract TuPeB4625.
100. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA.* 2001;285(9):1155-1163.
101. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
102. Moyle GJ. Where now for Trizivir? Role of the triple-NRTI pill post-ACTG 5095. *AIDS Read.* 2003;13(5):223-224, 227, 244.
103. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
104. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS.* 2003;17(7):987-999.
105. Balestre E, Dupon M, Capdepont S, et al. Virological response to HIV-1 nucleoside/nucleotide reverse transcriptase inhibitors-based, tenofovir DF-including regimens in the ANRS Aquitaine Cohort. *J Clin Virol.* 2006;36(2):95-99.
106. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
107. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. Paper presented at: 11th conference on retroviruses and opportunistic infections; February, 2004; San Francisco, CA.
108. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS.* 2006;20(10):1391-1399.
109. Kline MW, Van Dyke RB, Lindsey JC, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team. *Pediatrics.* 1998;101(2):214-220.
110. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.
111. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.

112. Borroto-Esoda K, Vela JE, Myrick F, et al. In vitro evaluation of the anti-HIV activity and metabolic interactions of tenofovir and emtricitabine. *Antivir Ther.* 2006;11(3):377-384.
113. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004;18(12):1691-1696.
114. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis.* 2004;39(7):1038-1046.
115. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
116. Phillips EJ. Genetic screening to prevent abacavir hypersensitivity reaction: are we there yet? *Clin Infect Dis.* 2006;43(1):103-105.
117. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
118. Stevens RC, Rodman JH, Yong FH, et al. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(5):415-421.
119. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.
120. Giacomet V, Mora S, Martelli L, et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40(4):448-450.
121. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):124-129.
122. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics.* 2005;116(6):e846-854.
123. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr.* 2008;47(1):74-78.
124. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* 2006;354(3):251-260.
125. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med.* 2009;361(23):2230-2240.
126. Loutfy MR, Ackad N, Antoniou T, et al. Randomized controlled trial of once-daily tenofovir, lamivudine, and lopinavir/ritonavir versus remaining on the same regimen in virologically suppressed HIV-infected patients on their first PI-containing HAART regimen. *HIV Clin Trials.* 2007;8(5):259-268.
127. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA.* 2004;292(2):191-201.
128. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J.* 2007;26(10):949-951.
129. Dieterich DT. Long-term complications of nucleoside reverse transcriptase inhibitor therapy. *AIDS Read.* 2003;13(4):176-184, 187.
130. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis.* 2002;34(6):838-846.
131. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS.* 2002;16(18):2447-2454.
132. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
133. Blanco F, Garcia-Benayas T, Jose de la Cruz J, et al. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials.* 2003;4(1):11-19.
134. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2304-2315.

135. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.

Monitoring of Children on Antiretroviral Therapy (Updated August 16, 2010)

Panel's Recommendations:

- ***Children who start a new antiretroviral regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure patient adherence to the regimen (AIII).***
- ***Children should be evaluated within 4 to 8 weeks to assess for possible side effects and to evaluate initial response to therapy (AIII). More frequent evaluation may be needed following initiation or change in therapy to support adherence to the regimen (AIII).***
- ***Subsequently, children should have a monitoring evaluation at least every 3 to 4 months to assess both efficacy and potential toxicity of their antiretroviral regimens (AII*).***

Children who start a new antiretroviral regimen or who change to a new regimen should be followed to assess effectiveness, adherence, tolerability, and side effects of the regimen. Frequent patient visits and intensive follow-up during the initial months after a new antiretroviral regimen is started are necessary to support and educate the family. The first few weeks of antiretroviral therapy can be particularly difficult for children and their caregivers. They must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience side effects of medications, and the child and caregivers need assistance in determining whether the effects are temporary and can be tolerated or whether they are more serious or long-term and necessitate a visit to the clinician. Thus, it is prudent for the clinician to assess the child within 1–2 weeks of initiating therapy, either in person or with a phone call, to assure proper administration of medications and to evaluate clinical concerns. Many clinicians will plan additional contact (in person or by telephone) with the child and caregivers during the first few weeks of therapy to support adherence.

Baseline laboratory assessments should be done prior to initiation of therapy; these include CD4 count/percentage and HIV RNA level; complete blood count and differential; serum chemistries (including electrolytes, BUN, creatinine, glucose, hepatic transaminases, calcium, and phosphorus); pancreatic enzyme evaluations (amylase, lipase) if therapy is being initiated with a drug with potential pancreatic toxicity, such as didanosine; and serum lipid evaluation (cholesterol, triglycerides). The child should be seen within 4–8 weeks after initiating or changing therapy to obtain a clinical history, with a focus on potential adverse effects and to assess adherence to medications; perform a physical examination; evaluate efficacy of therapy (measurement of CD4 count/percentage and HIV RNA levels); and obtain a laboratory evaluation for toxicity. More frequent evaluation may be needed following a change in therapy to support adherence to the regimen. At a minimum, laboratory assessments should include a complete blood count and differential, serum chemistries, and assessment of renal and hepatic function. Assessment of initial virologic response to therapy is important because an initial decrease in HIV viral load in response to antiretroviral treatment should be observed after 4–8 weeks of therapy.

Subsequently, children taking antiretroviral medication should have assessments of adherence, toxicity, and efficacy at least every 3–4 months. **Table 15** provides one proposed monitoring schema, which will require adjustment based on the specific therapy the child is receiving. Assessments should include basic hematology, chemistry, CD4 count/percentage, and HIV viral load. Monitoring of drug toxicities should be tailored to the particular medications the child is taking; for example, periodic monitoring of pancreatic enzymes may be desirable in children receiving didanosine, or of serum glucose and lipids in patients receiving PIs. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (e.g., evaluation of serum lactate in a child receiving NRTI drugs who develops symptoms suspicious for lactic acidosis) performed more frequently until the toxicity resolves. For further details of adverse effects associated with particular

antiretroviral medications, please see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**.

Table 15. Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy

Time Schedule for Monitoring	Toxicity Monitoring[1]	Efficacy and Adherence Monitoring
Baseline (prior to initiation of therapy)	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage, HIV RNA
1–2 weeks[2]	Clinical history	Adherence screen
4–8 weeks	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage[4], HIV RNA, adherence screen
Every 3–4 months	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage, HIV RNA, adherence screen
Every 6–12 months	Lipid panel	

[1] For children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3 to 4 months.

[2] Children starting a new antiretroviral regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure patient adherence to the regimen. Many clinicians will plan additional contacts (in person or by telephone) with the child and caregivers to support adherence during the first few weeks of therapy. Some clinicians also recommend an HIV RNA measurement within the initial weeks of therapy for an early assessment of response/adherence to therapy.

[3] Chemistries may include electrolytes, glucose, liver function tests (hepatic transaminases and bilirubin), renal function tests (BUN, creatinine), calcium, and phosphate. Additional evaluations should be tailored to the particular drugs the child is receiving; for example, pancreatic enzymes (amylase and lipase) may be considered if the child is starting drugs with potential pancreatic toxicity, such as didanosine.

[4] Some clinicians do not recommend a CD4 cell count/percentage at this time, considering it too early to expect an immunologic response.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated August 16, 2010)

***Panel's Recommendations*:**

- ***Antiretroviral therapy regimens must be individually tailored to the adolescent because those with perinatal exposure generally have a very different clinical course and treatment history than those who acquired HIV during adolescence (AIII).***
- ***Appropriate dosing of antiretroviral medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and chronologic age (AII).***
- ***Effective and appropriate contraceptive methods should be selected to reduce the likelihood of unintended pregnancy and prevent transmission of HIV (AI).***
- ***Providers should be aware of potential interactions between antiretroviral drugs and hormonal contraceptives, which could lower contraceptive efficacy (AII*).***
- ***Efavirenz should be avoided for the adolescent girl who desires to become pregnant or who does not use effective and consistent contraception (AII). Efavirenz also should be avoided throughout the first trimester of pregnancy (AII).***
- ***Pediatric and adolescent care providers should work with older adolescent patients to prepare them for transition into adult care settings (AIII).***

BACKGROUND

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive antiretroviral treatment history. Adolescents with behaviorally acquired infection (i.e., infection acquired via sexual activity or intravenous substance use) generally follow a clinical course that is similar to that of adults; they are in an earlier stage of infection, making them potential candidates for early intervention *[1]*.

DOSING OF ANTIRETROVIRAL THERAPY FOR HIV-INFECTED ADOLESCENTS

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics, which is especially important for drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors *[2]*. Dosages of medications for HIV infection and opportunistic infections traditionally have been prescribed according to Tanner staging of puberty *[3]* rather than strictly on the basis of age *[1]*. Using this method, adolescents in early puberty (Tanner stages I and II) are administered doses using pediatric schedules, whereas those in late puberty (Tanner stage V) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. In addition, puberty may be delayed in perinatally HIV-infected children *[4]*, adding to discrepancies between Tanner stage-based dosing and age-based dosing.

Many antiretroviral medications (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some PIs) are administered to children at higher weight- or surface area-based doses than would be predicted by direct scaling of adult doses, based upon reported pharmacokinetic data indicating higher oral drug clearance in children. Continued use of these pediatric weight- or surface area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every antiretroviral medication for adolescents are not available; **Appendix B: Pediatric Antiretroviral Drug Information** includes discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available. Other factors, such as toxicity, pill

burden, adherence, and virologic and immunologic parameters, may also help determine when to transition adolescents from pediatric to adult doses.

ADOLESCENT CONTRACEPTION, PREGNANCY, AND ANTIRETROVIRAL THERAPY

Adolescents with HIV infection, regardless of mode of acquisition, may be sexually active. Contraception methods and safer sex techniques for prevention of HIV transmission should be discussed with them regularly (see **Incorporating HIV Prevention into the Medical Care of Persons Living with HIV**) *[5]*.

The possibility of planned or unplanned pregnancy should be a consideration when selecting an antiretroviral regimen for the adolescent girl. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. Efavirenz-containing regimens should be avoided in adolescent girls who are trying to conceive or are not using effective and consistent contraception because of the potential for teratogenicity with fetal exposure to efavirenz in the first trimester.

Contraceptive-Antiretroviral Drug Interactions

Several PI and NNRTI drugs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)*** available at **http://aidsinfo.nih.gov** *[6]*. These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered in cases in which there are documented interactions. It is unknown whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot methoxyprogesterone acetate [DMPA]) would be compromised because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered among women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional side effects, and no clinically significant changes in antiretroviral drug levels *[7-8]*. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Adolescents who express a desire to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy (see Health and Human Services [HHS] ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** available at **http://aidsinfo.nih.gov** *[9]*).

Pregnant Adolescents

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant adults or adolescents. Details regarding choice of antiretroviral regimen in pregnant HIV-infected women, including adolescents, are provided in HHS ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** available at **http://aidsinfo.nih.gov** *[9]*.

TRANSITION OF ADOLESCENTS INTO ADULT HIV CARE SETTINGS

Facilitating a smooth transition for adolescents with any chronic health condition from the child or adolescent health system to one devoted to the care of adults can be difficult and is especially so for adolescents infected with HIV. Transition is described as “a multifaceted, active process that attends to the medical, psychosocial,

and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system" *[10]*. HIV care models for children and perinatally infected adolescents tend to be family centered, with input from members of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, more intimate settings. Although expert care is also provided in the adult HIV care medical model, the adolescent may feel unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers who often do not have a long-standing relationship with the adolescent. Providing support and guidance to the adolescent and to the adult medical care provider as to what is expected from each may be helpful. Some general guidelines about transitional plans and who might best benefit from them are available *[11-12]*. Pediatric and adolescent programs may benefit from the establishment of formal programs to introduce adolescents to the adult care setting.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
2. Rogers A. Pharmacokinetics and pharmacodynamics in adolescents. January 20-21, 1994. Proceedings. *J Adolesc Health.* 1994;15(8):605-678.
3. Schneider MB. Physical examination. In: Friedman SB, Fisher MM, Schoenberg SK, Alderman EM, eds. Comprehensive adolescent health care. 2nd ed. St. Louis, MO: Mosby-Year Book, Inc.1998:69-80.
4. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr.* 2003;33(1):56-65.
5. Centers for Disease Control and Prevention (CDC). Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
6. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care.* 2008;13(2):123-132.
7. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception.* 2008;77(2):84-90.
8. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. 2007;81(2):222-227.
9. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
10. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. *Pediatrics.* 2005;115(1):112-120.
11. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics.* 2002;110(6 Pt 2):1304-1306.
12. Rosen DS, Blum RW, Britto M, et al. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. *J Adolesc Health.* 2003;33(4):309-311.

Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated August 16, 2010)

Panel's Recommendations:

- ***Strategies to maximize adherence should be discussed prior to initiation of antiretroviral therapy and again when changing regimens (AIII).***
- ***Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence (AIII).***
- ***At least one method of measuring adherence to antiretroviral therapy (e.g., quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load (AII).***
- ***When feasible, once-daily antiretroviral regimens should be prescribed (AI*).***
- ***Maintain a nonjudgmental attitude, establish trust, and identify mutually acceptable goals for care (AII*).***

BACKGROUND

Medication adherence is fundamental to successful antiretroviral therapy. Adherence is a major factor in determining the degree of viral suppression achieved in response to antiretroviral therapy *[1-4]*. Poor adherence can lead to virologic failure. Prospective adult and pediatric studies have shown the risk of virologic failure to increase as the proportion of missed doses increases *[2, 5-7]*. Subtherapeutic antiretroviral drug levels resulting from poor adherence may facilitate the development of drug resistance to one or more drugs in a given regimen as well as possible cross resistance to other drugs in the same class. Therefore, in addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens for patients who develop drug-resistant viral strains.

Evidence indicates that adherence problems occur frequently in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to their regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), antiretroviral regimens, and study characteristics *[3-4, 8-11]*. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial characteristics of the child and parent, have been associated with adherence, but no clear predictors of either good or poor adherence in children have been consistently identified *[7-8, 10, 12-16]*. These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence education, support, and assessment integral components of care.

SPECIFIC ADHERENCE ISSUES IN CHILDREN

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient factors, and characteristics of health care providers *[14-15]*. Limited availability of palatable formulations for young children is especially problematic *[5, 17]*. Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments as well as the ability and willingness of the child to take the drug. Barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal *[18]*. Some caregivers may place too much responsibility on older children for managing medications before they are developmentally able to take on such tasks *[19]*. Many other barriers to adherence exist for children with HIV infection. For example, caregivers' unwillingness to disclose the child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling medications to maintain

secrecy within the household, reduction of social support, and a tendency to skip doses when the parent is away from the home or when the child is at school.

SPECIFIC ADHERENCE ISSUES FOR ADOLESCENTS

HIV-infected adolescents also face specific adherence challenges *[7, 20-22]*. Several studies have identified pill burden as well as lifestyle issues (not carrying medication, change in schedule) as barriers to complete adherence *[7, 20]*. Denial and fear of their HIV infection is common, especially in recently diagnosed youth; this may lead to refusal to initiate or continue antiretroviral therapy. Distrust of the medical establishment, misinformation about HIV, and a lack of knowledge about the availability and effectiveness of antiretroviral treatments can all be barriers to linking adolescents to care and maintaining successful antiretroviral therapy. Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they may have long histories of inadequate adherence. Regimen fatigue has also been identified as a barrier to adherence in adolescents *[23]*. Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, may have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness due to a lack of familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease stage all correlate with nonadherence *[21, 24]*. In a study of 833 HIV-infected Medicaid beneficiaries age 12–17 years, youth diagnosed with a psychiatric comorbidity (substance abuse, conduct disorder, or emotional disorder) were less likely to be receiving combination therapy; however, for those on therapy, only a conduct disorder diagnosis was associated with lower adherence *[25]*. A review of published papers on adherence among HIV-infected youth, however, suggests that depression and anxiety have been consistently associated with poorer adherence *[24]*. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties face adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and those who are homeless and have no place to store medicine. Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to antiretroviral treatment have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers and alarm devices, are well accepted by some youth. Small, discreet pillboxes in which to store medications in an organized fashion may be useful *[26]*. In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post intervention but the effect was not sustained at follow-up. Pager messaging was not associated with reported adherence but improved biologic outcomes were measured *[27]*. Another study evaluating the efficacy of a 4-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months among youth taking antiretroviral therapy at 6 months. However, reduction in viral load was not maintained at 9 months *[28]*.

ADHERENCE ASSESSMENT AND MONITORING

The process of adherence preparation and assessment should begin before therapy is initiated or changed, and a routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom antiretroviral treatment initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by the child and family and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership in medication management. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain explicit agreement with the treatment plan, including strategies to support adherence.

Adherence is difficult to assess accurately; different methods of assessment have been shown to yield different results, and each approach has limitations *[29-31]*. Both caregivers and health care providers often

overestimate adherence. Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multidrug-resistant virus. Other measures include quantitative self-report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed *[32]*. Also, targeted questions about stress, pill burden, and daily routine are recommended *[7-8, 29]*. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports *[33]*. Electronic monitoring devices, such as Medication Event Monitoring System (MEMS) caps, which record opening of medication bottles on a computer chip in the cap *[34]*, have been shown to be useful tools to measure adherence in some settings *[33, 35-36]*. Home visits can play an important role in assessing adherence and, in some cases, suspected nonadherence is confirmed only when dramatic clinical responses to antiretroviral therapy occur during hospitalizations or in other supervised settings *[37-40]*. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence *[41]*.

It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Furthermore, adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both the HIV-infected child and caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources *[42-43]*.

STRATEGIES TO IMPROVE AND SUPPORT ADHERENCE

Intensive follow-up is required, particularly during the critical first few months after therapy is started; patients should be seen frequently to assess adherence and determine the need for strategies to improve and support adherence. Strategies include development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers—rather than one specific intervention—may be most effective *[44-47]*. Although quite labor intensive, programs designed to administer directly observed combination therapy to adults in either the clinic or at home have demonstrated successful results in both the United States and in international, resource-poor settings *[48-52]*. In particular, modified directly observed therapy (m-DOT) when one dose is administered in a supervised setting and the remaining portions are self-administered appears to be both feasible and acceptable *[47]*. **Table 16** summarizes some of the strategies that can be used to support and improve adherence to antiretroviral medications.

Regimen-Related Strategies

Highly active antiretroviral regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects *[53]*. When nonadherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it may be simplified. For example, when the burden of pills is great, one or more drugs can be changed to result in a regimen containing fewer pills and potentially greater adherence. Several studies in adults have demonstrated better adherence in once-daily compared with twice-daily antiretroviral regimens *[54-56]*. When nonadherence is related to poor palatability of a liquid formulation or crushed pills, the offending taste may be masked by a small amount of flavoring syrups or food, as long as the medication is not

one with contraindications to simultaneous administration of food (see **Appendix B: Pediatric Antiretroviral Drug Information**), or the child may be taught to swallow pills in order to overcome medication aversion *[57]*.

Child/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient/caregiver education. Educating families about adherence should begin before antiretroviral medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining the child's medication adherence. Caregivers should understand that the first antiretroviral regimen has the best chance of long-term success. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into the HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence *[58-60]*. Training children on swallowing pills has been associated with improved adherence at 6 months post-training in a small study of children age 4 to 21 *[61]*. Availability of mental health services and treatment of mental health disorders may also facilitate adherence to complex antiretroviral regimens. For nonadherent children who are at risk of disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered *[62]*. Home nursing interventions may also be beneficial where adequate resources are available *[63]*. Directly observed dosing of antiretroviral medications has been implemented in adults and pediatrics with promising results *[48-52, 64]*, and such an approach has been implemented in some pediatric HIV programs, using home nursing services as well as daily medication administration in the clinic setting. Other strategies to support adherence that have been employed in the clinical setting include setting patient cell phones to alarm when medications are due to be taken, providing pill boxes and other adherence support tools, and weekly filling of pill boxes by nursing or pharmacy staff particularly for patients with complex regimens.

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with the families. This process begins early in the provider's relationship with the family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important *[65-67]*. Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child centered and includes caregivers in adherence support has also been shown to improve treatment outcomes *[68]*.

Table 16. Strategies to Improve Adherence with Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on need for treatment and adherence. • Identify depression, low self-esteem, drug use, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat prior to starting antiretroviral drugs, if possible. • Identify family, friends, health team members, or others who can help with adherence support. • Educate patient and family about the critical role of adherence in therapy outcome. • Specify the adherence target: ≥95% of prescribed doses. • Educate patient and family about the relationship between partial adherence and resistance. • Educate patient and family about resistance and constraint of later choices of antiretroviral drug (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent). • Develop a treatment plan that the patient and family understand and to which they feel committed. • Establish readiness to take medication by practice sessions or other means. • Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency and number of pills. • Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities. • Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability). • Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug-drug interactions. • Assess pill swallowing capacity and offer pill swallowing training.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter as needed. • Provide ongoing support, encouragement, and understanding of the difficulties of the demands of attaining ≥95% adherence with medication doses. • Use patient education aids including pictures, calendars, and stickers. • Use pill boxes, reminders, alarms, pagers, and timers. • Provide follow-up clinic visits or telephone calls to support and assess adherence. • Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence. • Provide pharmacist-based adherence support. • Consider gastrostomy tube use in selected circumstances. • Consider a brief period of hospitalization for selected circumstances of apparent virologic failure to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy. • Consider directly observed therapy at home, in the clinic, or during a brief inpatient hospitalization.

References

1. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
3. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics.* 2002;109(4):e61.
4. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 1999;18(8):682-689.
5. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
6. Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS.* 2002;16(16):2175-2182.
7. Murphy DA, Sarr M, Durako SJ, et al. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Arch Pediatr Adolesc Med.* 2003;157(3):249-255.
8. French T, Weiss L, Waters M, et al. Correlation of a brief perceived stress measure with nonadherence to antiretroviral therapy over time. *J Acquir Immune Defic Syndr.* 2005;38(5):590-597.
9. Katko E, Johnson GM, Fowler SL, et al. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(12):1174-1176.
10. Mellins CA, Brackis-Cott E, Dolezal C, et al. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(11):1035-1041.
11. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2000;19(12):1148-1153.
12. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics.* 2006;118(6):e1745-1757.
13. Malee K, Williams PL, Montepiedra G, et al. The role of cognitive functioning in medication adherence of children and adolescents with HIV infection. *J Pediatr Psychol.* 2009;34(2):164-175.
14. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep.* 2009;6(4):194-200.
15. Marón G, Herr M, Gaur A, et al. Adherence rates in adolescents prescribed once daily and twice daily doses of highly active antiretroviral therapy (HAART). Paper presented at: St. Jude/PIDS Research Conference; 2008; Memphis, TN.
16. Filho LF, Nogueira SA, Machado ES, et al. Factors associated with lack of antiretroviral adherence among adolescents in a reference centre in Rio de Janeiro, Brazil. *Int J STD AIDS.* 2008;19(10):685-688.
17. Gibb DM, Goodall RL, Giacomet V, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J.* 2003;22(1):56-62.
18. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS.* 2008;22(8):637-647.
19. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol.* 2009;34(2):187-194.
20. Belzer ME, Fuchs DN, Luftman GS, et al. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health.* 1999;25(5):316-319.
21. Murphy DA, Belzer M, Durako SJ, et al. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med.* 2005;159(8):764-770.
22. Rudy BJ, Murphy DA, Harris DR, et al. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS.* 2009;23(3):185-194.
23. Merzel C, Vandevanter N, Irvine M. Adherence to antiretroviral therapy among older children and adolescents with HIV: a qualitative study of psychosocial contexts. *AIDS Patient Care STDS.* 2008;22(12):977-987.
24. Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med.* 2009;17(1):14-25.

25. Walkup J, Akincigil A, Bilder S, et al. Psychiatric diagnosis and antiretroviral adherence among adolescent Medicaid beneficiaries diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome. *J Nerv Ment Dis.* 2009;197(5):354-361.
26. AIDS Institute New York State Department of Health. Supportive care issues for children with HIV infection. 2001; www.hivguidelines.org/GuidelineDocuments/p-suppcare.pdf.
27. Simoni JM, Huh D, Frick PA, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2009;52(4):465-473.
28. Naar-King S, Parsons JT, Murphy DA, et al. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. *Arch Pediatr Adolesc Med.* 2009;163(12):1092-1098.
29. Wiener L, Riekert K, Ryder C, et al. Assessing medication adherence in adolescents with HIV when electronic monitoring is not feasible. *AIDS Patient Care STDS.* 2004;18(9):527-538.
30. Davies MA, Boulle A, Fakir T, et al. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. *BMC Pediatr.* 2008;8:34.
31. Farley JJ, Montepiedra G, Storm D, et al. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count. *J Dev Behav Pediatr.* 2008;29(5):377-384.
32. Allison SM, Koenig LJ, Marhefka SL, et al. Assessing medication adherence of perinatally HIV-infected children using caregiver interviews. *J Assoc Nurses AIDS Care.* 2010.
33. Farley J, Hines S, Musk A, et al. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. *J Acquir Immune Defic Syndr.* 2003;33(2):211-218.
34. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm.* 1991;48(9):1978-1988.
35. Bova CA, Fennie KP, Knafl GJ, et al. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. *AIDS Behav.* 2005;9(1):103-110.
36. Muller AD, Bode S, Myer L, et al. Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa. *Pediatr Infect Dis J.* 2008;27(3):257-262.
37. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(7):716-718.
38. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. *AIDS Patient Care STDS.* 2006;20(4):275-284.
39. Roberts GM, Wheeler JG, Tucker NC, et al. Nonadherence with pediatric human immunodeficiency virus therapy as medical neglect. *Pediatrics.* 2004;114(3):e346-353.
40. Glikman D, Walsh L, Valkenburg J, et al. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. *Pediatrics.* 2007;119(5):e1142-1148.
41. van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(8):743-747.
42. Dolezal C, Mellins C, Brackis-Cott E, et al. The reliability of reports of medical adherence from children with HIV and their adult caregivers. *J Pediatr Psychol.* 2003;28(5):355-361.
43. Podsadecki TJ, Vrijens BC, Tousset EP, et al. "White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. *HIV Clin Trials.* 2008;9(4):238-246.
44. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet.* 1996;348(9024):383-386.
45. Winnick S, Lucas DO, Hartman AL, et al. How do you improve compliance? *Pediatrics.* 2005;115(6):e718-724.
46. Wu AW, Ammassari A, Antinori A. Adherence to antiretroviral therapy: where are we, and where do we go from here? *J Acquir Immune Defic Syndr.* 2002;31 Suppl 3:S95-97.
47. Simoni JM, Amico KR, Pearson CR, et al. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. *Curr Infect Dis Rep.* 2008;10(6):515-521.
48. Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis.* 2004;38 Suppl 5:S429-436.

49. Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr.* 2004;36(4):929-934.
50. Jayaweera DT, Kolber MA, Brill M, et al. Effectiveness and tolerability of a once-daily amprenavir/ritonavir-containing highly active antiretroviral therapy regimen in antiretroviral-naive patients at risk for nonadherence: 48-week results after 24 weeks of directly observed therapy. *HIV Med.* 2004;5(5):364-370.
51. Williams AB, Fennie KP, Bova CA, et al. Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2006;42(3):314-321.
52. Myung P, Pugatch D, Brady MF, et al. Directly observed highly active antiretroviral therapy for HIV-infected children in Cambodia. *Am J Public Health.* 2007;97(6):974-977.
53. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS.* 2009;23(10):803-807.
54. Boyle BA, Jayaweera D, Witt MD, et al. Randomization to once-daily stavudine extended release/lamivudine/efavirenz versus a more frequent regimen improves adherence while maintaining viral suppression. *HIV Clin Trials.* 2008;9(3):164-176.
55. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses.* 2007;23(12):1505-1514.
56. Parienti JJ, Bangsberg DR, Verdon R, et al. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis.* 2009;48(4):484-488.
57. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader.* 2000;10(2):88-94.
58. AIDS Institute New York State Department of Health. Promoting adherence to antiretroviral therapy. 2001; http://www.hivguidelines.org/quality-of-care/best-practices/promoting-adherence-to-antiretroviral-therapy/.
59. DiIorio C, Resnicow K, McDonnell M, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a pilot study. *J Assoc Nurses AIDS Care.* 2003;14(2):52-62.
60. Hammami N, Nostlinger C, Hoeree T, et al. Integrating adherence to highly active antiretroviral therapy into children's daily lives: a qualitative study. *Pediatrics.* 2004;114(5):e591-597.
61. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics.* 2007;119(4):e893-899.
62. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics.* 2000;105(6):E80.
63. Berrien VM, Salazar JC, Reynolds E, et al. Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention. *AIDS Patient Care STDS.* 2004;18(6):355-363.
64. Mitty JA, Stone VE, Sands M, et al. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. *Clin Infect Dis.* 2002;34(7):984-990.
65. Tugenberg T, Ware NC, Wyatt MA. Paradoxical effects of clinician emphasis on adherence to combination antiretroviral therapy for HIV/AIDS. *AIDS Patient Care STDS.* 2006;20(4):269-274.
66. Wang X, Wu Z. Factors associated with adherence to antiretroviral therapy among HIV/AIDS patients in rural China. *AIDS.* 2007;21 Suppl 8:S149-155.
67. Molassiotis A, Morris K, Trueman I. The importance of the patient-clinician relationship in adherence to antiretroviral medication. *Int J Nurs Pract.* 2007;13(6):370-376.
68. Van Winghem J, Telfer B, Reid T, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. *BMC Pediatr.* 2008;8:52.

Management of Medication Toxicity or Intolerance (Updated August 16, 2010)

Panel's Recommendations:

- ***If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately (AIII). Once the symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different antiretroviral drug or drugs for the offending agent(s) (AII*).***
- ***When changing therapy because of toxicity or intolerance to a specific drug in a virally suppressed individual, changing a single drug in a multi-drug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen (AI*).***
- ***The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity to facilitate future medication choices if care is transferred (AIII).***
- ***Dose reduction is not a recommended option in the setting of antiretroviral toxicity except when therapeutic drug monitoring indicates a drug concentration above the normal therapeutic range (AII*).***

Side effects or intolerance of antiretroviral agents occur with moderate frequency and should prompt a re-evaluation of the antiretroviral regimen. Drug-related toxicity may be acute, occurring soon after a drug has been administered; subacute, occurring within 1−2 days of administration; or late, occurring after prolonged drug administration. Such adverse events may vary in severity from mild to severe and life threatening (see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**).

Identification of the responsible agent may allow for substitution of a similar agent to which the patient's virus is sensitive. Knowledge of the patient's prior antiretroviral history and, if possible, viral resistance profile prior to the current course of antiretroviral therapy is essential. Any new agent used should be assessed for likely effectiveness against the patient's virus and for possible interactions with the other medications the patient will take.

Experience with antiretroviral drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain antiretroviral drugs or drug classes (see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**).

The physician, patient, and caregiver should discuss the response to a medication-related toxicity, taking into account the severity of toxicity, the relative need for viral suppression, and the available antiretroviral options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution; symptomatic treatment may be given, such as antihistamines for a mild rash. For some moderate toxicities, substituting the toxicity-associated antiretroviral drug with a drug in the same drug class but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required. Severe, life-threatening toxicity requires discontinuation of all antiretroviral drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity). Another drug can be substituted for the drug associated with the toxicity once the patient is stabilized and the toxicity is resolved.

When a patient experiences an unacceptable adverse effect from antiretroviral therapy every attempt should be made to identify the offending agent and replace the drug with another effective agent to minimize the amount of time a patient is on suboptimal therapy. For example, if therapy needs to be stopped due to a severe or life-threatening side effect, all antiretroviral drugs should be stopped. Once the offending drug or alternative cause for the adverse event has been determined, planning can begin for resumption of therapy with a new antiretroviral drug regimen that does not contain the offending drug or with the original regimen if the event is attributable to another cause. All drugs in the antiretroviral regimen should then be started simultaneously, rather than starting them one at a time and observing for adverse effects. Many experts recommend stopping

efavirenz or nevirapine several days before stopping other drugs, if possible, because these drugs have a significantly longer half-life than NRTI antiretroviral drugs. However, if a patient has a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

When therapy is changed because of toxicity or intolerance in the context of virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible. Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multi-drug regimen is a permissible option. For a patient who is not virally suppressed, a single drug substitution with an active agent is generally not recommended due to concern for development of resistance (see **Approach to the Management of Antiretroviral Treatment Failure**).

Therapeutic drug monitoring (TDM) is not available on a routine basis to most clinicians, and the settings in which TDM is useful are unclear, especially in children. One such setting, however, may be in the context of a child with mild or moderate toxicity possibly attributable to a particular antiretroviral agent (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**). In this situation, it is reasonable for the clinician to use TDM (if available) to determine if the toxicity is due to a concentration of drug exceeding the normal therapeutic range. This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then it should be used with caution.

Management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change from one drug to another drug to which the patient's virus is sensitive (e.g., change to stavudine for zidovudine-related anemia or to nevirapine for efavirenz-related central nervous system symptoms).
- Change in drug class, if necessary (e.g., from a PI to an NNRTI or vice versa) and if the patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations describe specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provide selected references regarding these toxicities in pediatric patients.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hematologic Effects:						
Anemia*	Principally ZDV	Onset: Variable, weeks to months Presentation: • Most commonly asymptomatic or mild fatigue, pallor, tachypnea • Rarely, congestive heart failure	HIV-exposed newborns: • Uncommon but coincident with physiologic Hgb nadir HIV-infected children on ARVs: • 2–3 times more common with ZDV-containing regimens • Less frequent in recent studies, possibly due to lower dosing of ZDV	HIV-exposed newborns: • Premature birth • *In utero* exposure to ARVs • Advanced maternal HIV disease • Neonatal blood loss HIV-infected children on ARVs: • Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) • Poorly controlled HIV • Marrow-toxic drugs (e.g., trimethoprim-sulfamethoxazole, rifabutin) • Iron deficiency	HIV-exposed newborns: • Monitor CBC at birth. • Consider repeat CBC at 4 weeks for higher risk babies (exposed to ARVs *in utero* or as neonates, premature birth, or low birth Hgb). HIV-infected children on ARVs: • Avoid ZDV in children with anemia when alternative agents are available. • Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: • Rarely require intervention unless Hgb is <7.0 gm/dL or anemia is associated with symptoms. • Consider discontinuing ZDV if ≥4 weeks of 6-week ZDV prophylaxis regimen are already completed. (see **Perinatal Guidelines**†). HIV-infected children on ARVs: • Discontinue non-ARV marrow-toxic drugs if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • Rarely necessary to discontinue ARV therapy. • For persistent anemia thought to be associated with ARVs: o change to a non-ZDV-containing regimen; o give erythropoietin 50–200 IU/kg/dose 3 times weekly.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia*	Principally ZDV	Onset: Variable Presentation: • Most commonly asymptomatic with ANC >500 cells/mm^3 • Associated with increased bacterial infections if ANC persistently <500 cells/mm^3	HIV-exposed newborns: • Rare HIV-infected children on ARVs: • 9.9%–26.8% of children on ARVs, depending upon the ARV regimen • Higher with ZDV-containing regimens	HIV-exposed newborns: • *In utero* exposure to ARVs HIV-infected children on ARVs: • Poorly controlled HIV infection • Marrow-toxic drugs (e.g., trimethoprim-sulfamethoxazole, ganciclovir, hydroxyurea, rifabutin)	HIV-infected children on ARVs: • Monitor CBC 3–4 times per year as part of routine care.	HIV-infected children on ARVs: • Intervention typically not necessary unless ANC <500 cells/mm^3 for prolonged periods or if associated with recurrent infections. • Discontinue non-ARV marrow-toxic drugs if feasible. • Treat coexisting OIs, malignancies. • Rarely necessary to discontinue ARV therapy. • For persistent neutropenia thought to be associated with ARVs: o change to a non-ZDV-containing regimen o give G-CSF 5–10 mcg/kg once daily (doses up to 20 mcg/kg have been used).

* HIV infection itself, opportunistic infections, and medications used to prevent OIs, such as trimethroprim-sulfamethoxazole, may all contribute to anemia, neutropenia, and thrombocytopenia.

† Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Key to Abbreviations: ANC = absolute neutrophil count; ARVs = antiretrovirals; CBC = complete blood count; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; IU = International Unit; OIs = opportunistic infections; ZDV = zidovudine

References

1. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. 1997;336(24):1704-12.
2. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse- transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-81.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-80.
4. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001.
5. McKinney RE Jr, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*. 1998;133(4):500-8.
6. Najean Y, Rain JD. The mechanism of thrombocytopenia in patients with HIV infection. *J Lab Clin Med*. 1994;123(3):415-20.
7. Caselli D, Maccabruni A, Zuccotti GV, et al. Recombinant erythropoietin for treatment of anaemia in HIV-infected children. *AIDS*. 1996;10(8):929-31.
8. Allen UD, Kirby MA, Goeree R. Cost-effectiveness of recombinant human erythropoietin versus transfusions in the treatment of zidovudine-related anemia in HIV-infected children. *Pediatr AIDS HIV Infect*. 1997;8(1):4-11.
9. Mueller BU, Jacobsen F, Butler KM, et al. Combination treatment with azidothymidine and granulocyte colony-stimulating factor in children with human immunodeficiency virus infection. *J Pediatr*. 1992;121(5 Pt 1):792-802.
10. Bussel JB, Graziano JN, Kimberly RP, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. *Blood*. 1991;77(9):1884-93.
11. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997;89(8):2689-700.

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatic Events:						
Hepatic toxicity (elevated AST, ALT, clinical hepatitis)	All ARVs	Onset: • *NNRTI and PI therapy*: Within 12 weeks of initiation. • *NRTI therapy*: Within months to years of initiation. • *Any antiretroviral combination regimen*: Early due to immune reconstitution inflammatory syndrome. Presentation: • Asymptomatic elevation of AST, ALT. • May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. • NRTIs, especially ZDV, ddI, d4T, may be associated with lactic acidosis and hepatic steatosis. • Rarely, prolonged exposure to ddI is associated with non-cirrhotic portal hypertension with esophageal varicies.	• Uncommon in children. • Frequency varies with different agents and drug combinations (NVP, TPV of particular concern).	• HBV or HCV coinfection • Elevated baseline ALT, AST • Other hepatotoxic medications • Alcohol use • Underlying liver disease • For NVP-associated hepatic events in adults: o female with pre-NVP CD4 >250 cells/mm^3 o male with pre-NVP CD4 >400 cells/mm^3 • Higher drug concentrations for PIs, particularly TPV	Prevention: Avoid concomitant use of hepatotoxic medications. Monitoring: *For ARVs other than NVP*: Obtain AST, ALT at baseline and at least every 3–4 months or more frequently in at-risk patients (e.g., HBV or HCV coinfected, elevated baseline AST, ALT). *For NVP*: Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.	• In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring. • If hepatic enzymes elevated >5–10 times ULN, most clinicians would avoid NVP. • In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent. • If a symptomatic hepatic event occurs on NVP, permanently discontinue NVP (see also NVP hypersensitivity). • When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, NRTIs, ZDV, d4T,

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• AST, ALT elevations while on NVP or ABC may be associated with a hypersensitivity reaction. • HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, TDF.				ddI in particular (see also lactic acidosis). • Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.
Indirect hyperbilirubinemia	IDV, ATV	Onset: Early in therapy. Presentation: • Jaundice. • Asymptomatic elevation of indirect bilirubin levels.	HIV-infected children receiving ATV: 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.	Not associated with HBV or HCV.	Monitoring: Assess bilirubin levels periodically, especially in first few months on regimen.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ALT = alanine transaminase; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; CMV = cytomegalovirus; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

References

1. Aceti A, Pasquazzi C, Zechini B, et al. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with hiv: The role of hepatitis b and c virus infection. *J Acquir Immune Defic Syndr*. 2002;29(1)**,** 41-8.
2. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5)**,** 538-9.
3. Busti AJ, Hall RgandMargolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmcotherapy*. 2004;24(12)**,** 1732-47.
4. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*. 2004;38(Suppl 2)**,** S80-9.

5. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis*. 2003;23(2)**,** 173-82.
6. Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus co-infection. *Clin Infect Dis*. 2010;50:502-11.
7. Kovari H, Ledergerber B, Peter U et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis*. 2009;49(4):626-635.
8. Levy V, Grant RM. Antiretroviral therapy for hepatitis b virus-hiv-coinfected patients: Promises and pitfalls. *Clin Infect Dis*. 2006;43(7)**,** 904-10.
9. Montessori V, Harris M, Montaner JS. Hepatotoxicity of nucleoside reverse transcriptase inhibitors. *Semin Liver Dis*. 2003;23(2)**,** 167-72.
10. Nunez M, Lana R, Mendoza JL, et al. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;27(5)**,** 426-31.
11. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: Intricacies of the pathogenic mechanisms. *Clin Infect Dis*. 2004;38(Suppl 2)**,** S65-72.
12. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: Incidence, liver histology, and outcome. *J Acquir Immune Defic Syndr*. 2003;32(3)**,** 259-67.
13. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of hiv infected patients. *J Acquir Immune Defic Syndr*. 2003;34(Suppl 1)**,** S21-33.
14. Sulkowski MS (2004) Drug-induced liver injury associated with antiretroviral therapy that includes hiv-1 protease inhibitors. *Clin Infect Dis,* 38(Suppl 2)**,** S90-7.
15. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198:1599-608.
16. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186(1)**,** 23-31.

Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, diabetes mellitus (DM)*	• Thymidine analogue NRTIs (d4T > ZDV) • Some PIs but unclear if class effect	Onset: Weeks to months after beginning therapy; median = 60 days (adult data) Presentation: • *Most commonly*: Asymptomatic fasting hyperglycemia, possibly in the setting of lipodystrophy, metabolic syndrome, or growth delay • *Also possible*: Frank DM (polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Impaired fasting glucose: • *ARV-treated adults*: 3%–25% • *ARV-treated children*: 0%–7% Impaired glucose tolerance: • *ARV-treated adults*: 16%–35% • *ARV-treated children*: 3%–4% DM: • *ARV-treated adults*: 1.2–4.7 per 100 person-years (2–4-fold greater than that for non-HIV-infected adults) • *ARV-treated children*: Very rare in HIV-infected children	Risk factors for Type 2 DM: • Lipodystrophy, metabolic syndrome • Family history of DM • Overweight, obesity	Prevention: • Lifestyle modification (see Management). • Although uncertain, avoiding use of d4T, PI-containing regimens might reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans. • Obtain random plasma glucose (RPG) levels at: o initiation of ARV therapy; o 3–6 months later; and o annually thereafter. • For RPG ≥140 mg/dL, obtain fasting plasma glucose (FPG) performed after 8-hour fast and consider referral to endocrinologist.	• Counsel lifestyle modification (low fat diet, exercise, no smoking). • Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen. • *For either RPG ≥200 mg/dL plus symptoms of DM or FPG ≥126 mg/dL*: Diagnostic criteria for DM are met; consult endocrinologist. • *FPG 100–125 mg/dL*: Impaired FPG is suggestive of insulin resistance; consult endocrinologist. • *FPG <100 mg/dL*: Suggests no current insulin resistance; recheck in 6–12 months.

***** Insulin resistance, asymptomatic hyperglycemia, and diabetes mellitus form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired fasting plasma glucose* (impaired FPG) as an FPG of 100–125 mg/dL; *impaired glucose tolerance* is an elevated 2-hour PG of 140–199 mg/dL in a standard oral glucose tolerance test (OGTT); and *diabetes mellitus* as either a FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, a HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, glycosylated hemoglobin A1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Abbreviations: ARV = antiretroviral; d4T = stavudine; DM = diabetes mellitus; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

References

Clinical features of hyperglycemia, insulin resistance, and diabetes mellitus

1. Amaya RA, Kozinetz CA, Mcmeans A, et al. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(5)**,** 405-10.
2. Arpadi SM, Cuff PA, Horlick M, et al. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ -lymphocyte count and CD4+ -lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *J Acquir Immune Defic Syndr*. 2001;27(1)**,** 30-4.
3. Beregszaszi M, Dollfus C, Levine M, et al. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. *J Acquir Immune Defic Syndr*. 2005;40(2)**,** 161-8.
4. Bitnun A, Sochett E, Babyn P, et al. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naive HIV-infected children. *AIDS*. 2003;17(9)**,** 1319-27.
5. Bitnun A, Sochett E, Dick PT, et al. Insulin sensitivity and beta-cell function in protease inhibitor-treated and -naive human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2005;90(1)**,** 168-74.
6. Bockhorst JL, Ksseiry I, Toye M, et al. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. *Pediatr Infect Dis J*. 2003;22(5)**,** 463-5.
7. Hadigan C. Insulin resistance among HIV-infected patients: Unraveling the mechanism. *Clin Infect Dis*. 2005;41(9)**,** 1341-2.
8. Leonard EG, McComsey GA. Antiretroviral therapy in HIV-infected children: The metabolic cost of improved survival. *Infect Dis Clin North Am*. 2005;19(3)**,** 713-29.
9. McComsey GA, Leonard E. Metabolic complications of HIV therapy in children. *AIDS*. 2004;18(13)**,** 1753-68.
10. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr*. 2000;23(1)**,** 35-43.
11. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: The price of success. *JAMA*. 2006;296(7)**,** 844-54.
12. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter aids cohort study. *Arch Intern Med*. 2006;165(10)**,** 1179-84.
13. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. 2003;32(3)**,** 298-302.

14. Abdel-Khalek I, Moallem HJ, Fikrig S, Castells S. New onset diabetes mellitus in an HIV-positive adolescent. *AIDS Patient Care STDS*. 1998;12(3)**,** 167-9.

15. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-72.

16. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. 2008;122(1):e129-38.

17. Blümer RM, van Vonderen MG, Sutinen J, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. *AIDS*. 2008;22(2):227-36.

18. Lee GA, Rao M, Mulligan K, et al. Effects of ritonavir and amprenavir on insulin sensitivity in healthy volunteers. *AIDS*. 2007;21(16):2183-90.

19. Tien PC, Schneider MF, Cole SR, et al. Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV study. *J Acquir Immune Defic Syndr*. 2008;49(4):369-76.

Management of hyperglycemia, insulin resistance, and diabetes mellitus

20. American Diabetes Association. Type 2 diabetes in children and adolescents (consensus statement). *Diabetes Care***.** 2000;23:381-9.

21. American Diabetes Association. Screening for type 2 diabetes (position statement). *Diabetes Care*. 2004;27(Suppl 1)**,** S11-S14.

22. American Diabetes Association. Standards of medical care in diabetes—2010 (position statement). *Diabetes Care*. 2010;33(Suppl 1):S11-61.

23. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association; European Association for Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.

24. Nathan DM, Davidson MB, DeFronzo RA, et al. (2007) Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*, 30(3):753-759.

25. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002;31(3)**,** 257-75.

26. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006;43(5)**,** 645-53.

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	PIs: All PIs; lower incidence with ATV NRTIs: Especially d4T	Onset: Weeks to months after beginning therapy Presentation: *PIs*: ↑LDL-C, TC, and TG *NNRTIs*: ↑LDL-C, TC, and HDL-C *NRTIs*: ↑LDL-C, TC, and TG	20%–50% of children receiving combination antiretroviral therapy will have lipoprotein abnormalities.	• HIV infection • Poor diet • Lack of exercise • Obesity • Hypertension • Smoking • Family history of dyslipidemia or premature CVD • Metabolic syndrome	Prevention: Low fat diet, exercise, no smoking. Monitoring: *Adolescents and adults*: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing ARV therapy, 3–6 months thereafter, then every 6–12 months. *Children without lipid abnormalities or risk factors*: Obtain nonfasting screening lipid profiles prior to initiating or changing therapy and every 6–12 months if stable. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with lipid abnormalities and/or additional risk factors*: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing therapy and every 6 months (or more often if indicated). *Children receiving lipid-lowering therapy with statins or fibrates*: Obtain fasting (12-hour) lipid profiles, liver function tests (LFTs), and creatine kinase (CK) prior to initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal	• Counsel lifestyle modification (low fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). • Switch to a new ARV regimen less likely to cause lipid abnormalities.[*] Pharmacologic Management: • Prompt intervention is required in patients with TG ≥500 mg/dL (high risk of pancreatitis). • Statins such as pravastatin or atorvastatin[†] • Fibrates such as gemfibrozil and fenofibrate may be used as alternative agents for adults with ↑TG but are not approved for use in children. • N-3 polyunsaturated fatty acids (PUFAs) derived from fish oils • No consensus as to what LDL-C should prompt treatment in children receiving ARVs [‡] o *High-risk patients*:

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
					alterations in AST, ALT, and CK, then every 3 months. Whenever doses of antihyperlipidemic agents are increased, repeat at 4 weeks.	Goal LDL-C ≤100 mg/dL o *Moderate-risk patients*: Goal LDL-C ≤130 mg/dL o *At-risk patients*: Goal LDL-C ≤160 mg/dL.

[*] The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

[†]Statins are teratogenic and should not be used in female patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins limited to children >6 years of age. Multiple drug interactions with lipid-lowering agents and ARVs.

Pravastatin (Pravachol)
8–13 years of age: 20 mg once daily; 14–18 years of age: 40 mg once daily

Atorvastatin (Lipitor)
>6 years of age: 10–20 mg once daily

[‡]It is unclear what the long-term risks of lipid abnormalities are in children receiving combination antiretroviral therapy. However, persistent dyslipidemia in children is likely to lead to premature cardiovascular disease.

Key to Abbreviations: ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; CVD = cardiovascular disease; d4T = stavudine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TC = total cholesterol; TG = triglycerides; ZDV = zidovudine

References

1. Cheseaux JJ, Jotterand V, Aebi C, et al. Hyperlipidemia in HIV-infected children treated with protease inhibitors: relevance for cardiovascular diseases. *J Acquir Immune Defic Syndr*. 2002;30(3):288-93.
2. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation*. 2007;115:1948-1967.
3. Lainka E, Oezbek S, Falck M, et al. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics*. 2002;110;e56.
4. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114: 2710-2738.

5. Kavey RE, Daniels SR, Lauer RM, et al. American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood. *Circulation*. 2003;107:1562-1566.
6. Belay B, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics*. 2007;119:370-0787.
7. Farley J, Gona P, Crain M, Cervia J, Oleske J, Seage III G, Lindsey J for the Pediatric AIDS Clinical Trials Study 219C Team. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4-19 years) in PACTG 219C. *J Acquir Immune Defic Syndr*. 2004;38:480-487.
8. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics*. 2003;111(3):e275-81.
9. De Truchis P, Kirkstetter M, Perier A, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy. A randomized prospective trial. *J Acquir Immune Defic Syndr*. 2007;44:278-285.
10. Engler MM, Engler MB, Malloy MJ, et al. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *Am J Cardiol*. 2005;95:869-871.
11. Gerber JG, Kitch DW, Fictenbaum CJ, et al. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy. Results of ACTG A5186. *J Acquir Immune Defic Syndr*. 2008;47:459-466.
12. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med*. 2006;355:2283-96.
13. The D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *New Engl J Med*. 2007;356:1723-35.
14. Vigano A, Adrovandi GM, Giacomet V, et al. Improvement in dyslipidemia after switching stavudine to tenofovir and replacing protease inhibitor with efavirenz in HIV-infected children. *Antiviral Therapy*. 2005;10:917-924.
15. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution, and hyperlipidemia in HIV-infected children in Europe. *AIDS*. 2004; 18:1443-1451.
16. Rhoads MP, Smith CJ, Tudor-Williams G, et al. Effects of HAART on pediatric metabolite levels. *HIV Med*. 2006; 7(1):16-24.
17. Carter RJ, Wiener J, Abrams EJ, et al. Dyslipidemia among perinatally HIV-infected children enrolled in the PACTS-HOPE cohort, 1999-2004: A longitudinal analysis. *J Acquir Immune Defic Syndr*. 2006; 41:453-460.
18. Tassiopoulos K, Williams PL, Seage GR, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2008; 47:607-614.
19. Daniels SR, Greer FR, and the committee on nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008; 122:198-208.
20. Kwiterovich PO. Recognition and management of dyslipidemia in children and adolescents. *J Clin Endocrinol Metab*. 2008; 93:4200-4209.
21. Currier JS. Update on cardiovascular complications in HIV infection. *Topics in HIV Medicine*. 2009;17: 98-103.
22. Dube M, Fenton M. Lipid abnornalities. *Clin Infect Dis*. 2003;36(Suppl 2):S79-83.

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Skin rash	NVP, EFV, ETR, FPV, ATV, FTC ABC, DRV, TPV, TDF, LPV/r, RAL, MVC	Onset: The first few days to weeks after starting therapy. Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions. Some rashes are a manifestation of systemic hypersensitivity (see also hypersensitivity reaction).	Common (>10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC Less common (5%–10%): ABC, DRV, TPV, TDF Unusual (2%–4%): LPV/r, RAL, MVC	• Rash with a sulfonamide is a risk factor for rash with NNRTIs and the PIs containing a sulfonamide moiety (FPV, APV, DRV, TPV). • Possible association of the HLA-DRB 101 allele with rash with NVP or EFV.	When starting NVP or restarting after interruptions ≥7 days: • Once-daily dosing for 2 weeks (50% of total daily dose), then escalation to target dose with twice-daily dosing is associated with fewer rashes.* • Avoid the use of corticosteroids during NVP dose escalation. • Assess patient for rash severity and presence of systemic signs and symptoms (see also hypersensitivity reaction).	Mild-to-moderate rash: • Prescribe antihistamine as needed; the antiretroviral medication can be continued.* Severe rash (accompanied by blisters, fever, involvement of the oral/anal mucous membranes, conjunctivitis, edema, arthralgias): • Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.) • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. • Measure hepatic transaminases if rash develops with NVP treatment. If hepatic transaminases are

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).
	ENF	Onset: The first few days to weeks after starting therapy. Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.	Adults: >90% (resulted in ENF discontinuation in 7%)	Unknown,	• During routine visits assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient, adjust injection technique, and rotate injection sites.
Stevens-Johnson syndrome (SJS)/ erythema multiforme major (EM)/toxic epidermal necrolysis (TEN)	NVP, EFV, ETR, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Onset: The first few days to weeks after initiating therapy. Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bullae formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, arthralgia.	Infrequent: NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case reports: FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Adults: • Female • Black • Asian • Hispanic.	• For NVP, 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may prevent the rash.* • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • May need intensive care support, intravenous hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics in case of superinfection. • Corticosteroids and/or IVIG are sometimes used but use of each is controversial. • Do not reintroduce the offending

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						medication. • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic hypersensitivity reaction (HSR) (with or without skin involvement)	ABC	Onset: Within the first 6 weeks with first use; within hours with reintroduction. Presentation: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. Symptoms can mimic anaphylaxis with rechallenge.	2.3%–9% (varies by racial/ethnic group)	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3. • Whites are at much greater risk of HSR than blacks or Asians.	• Screen for HLA-B*5701. • ABC should not be prescribed if HLA-B*5701 is positive. The patient should be labeled as ABC allergic in the medical record. • Counsel families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms such as an intercurrent viral illness. Treat symptoms as necessary. • Most symptoms resolve by 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.
	NVP	Onset: Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or	4% (2.5%–11%)	For adults: • Treatment naïve with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm3 in men) • Females 3-fold higher risk than males • NVP	• 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.*	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and close monitoring. • Do not reintroduce NVP. The safety of other NNRTIs is

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been described.		hepatoxicitiy and hypersensitivity may be less common in prepubertal children than in adults.	• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT in patients with rash. • Obtain AST and ALT at baseline, prior to dose escalation, 2 weeks post dose escalation, and at 3-month intervals thereafter. • Avoid use in women with CD4 >250 cells/mm^3 and in men with CD4 >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in postexposure prophylaxis.	unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
	ENF	Onset: Any time during therapy. Presentation: Symptoms may include rash, fever, nausea, vomiting, rigors, hypertension, elevated hepatic transaminases.	<1%	Unknown.	• Evaluate for hypersensitivity if the patient is symptomatic.	• Discontinue ARVs. • Rechallenge with ENF is not recommended.

* The prescribing information for nevirapine states that patients experiencing rash during the 14-day lead-in period should not have the nevirapine dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase the risk of nevirapine resistance due to subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. Nevirapine should be stopped if the rash is severe or is worsening or progressing.

Key to Abbreviations: ABC = abacavir; ALT = alanine transaminase; APV = amprenavir; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; ddI = didanosine; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FTC = emtricitabine; FPV = fosamprenavir; HSR = hypersensitiviy reaction; IDV = indinavir; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; SJS = Stevens Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

References

1. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. 12th Conference on Retrovirues and Opportunistic Infections; February 22-25, 2005; Boston, MA. Abstract 776.
2. Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chem*. 2008;62,879-888.
3. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet*. 2000;356,1423-1430.
4. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. *J Allergy Clin Immunol*. 2008;121,826-32.
5. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359,727-732.
6. Mallal S, Phillips E, Carosi G, et al. HLA_B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358,568-579.
7. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet*. 2000;39,281-293.
8. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV-infected patients. *J Acquir Immune Defic Syndr*. 2003;35,538-539.
9. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatol*. 2003;206,353-6.
10. Trottier, B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. *J Acquir Immune Defic Syndr*. 2005;40(4):413-21.
11. Vitezica ZG, Milpied B, Lonjou C, et el. HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS*. 2008;22(4):540-1.

Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lipodystrophy, Lipohypertrophy, Lipoatrophy

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy—General information		Onset: Trunk and limb fat initially increases within a few months of start of ART; however, peripheral fat wasting may not begin to appear for 12–24 months.	Adults: 2%–84% Children: 1%–33%, perhaps more common in adolescents than prepubertal children	• Genetic predisposition • Puberty • HIV-associated inflammation		
Central lipohypertrophy	• Most associated with PIs and EFV • Can occur in the absence of ART	Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy). In adults, waist circumference >102 cm (men) or >88 cm (women) is associated with increased risk of metabolic syndrome. For children and adolescents, waist circumference above the 75% percentile for age is associated with increased risk of metabolic syndrome.	See above	• PIs • EFV	Prevention: Diet and exercise. Monitoring: Measure waist circumference, waist to height ratio, and/or BMI (increase of each associated with development of metabolic syndrome).	• Diet and exercise, especially strength training. • Liposuction (Lipohypertrophy may reoccur after this cosmetic procedure; liposuction is not recommended for children.) • Recombinant human growth hormone or growth hormone-releasing hormone (investigational). • Metformin and rosiglitazone are not useful for treatment.

Facial/peripheral lipoatrophy	Most associated with thymidine analogue NRTI (d4T > ZDV)	Presentation: Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Risk low in patients not treated with d4T or ZDV	• d4T and ZDV • Obesity prior to ART	Prevention: Avoid use of d4T and ZDV. Monitoring: Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	• Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. • Poly-L-lactic acid is FDA approved for injection into areas of facial lipoatrophy in adults but difficult to use. Use is not reported for children. • Recombinant human leptin (investigational).

Key to Abbreviations: ART = antiretroviral therapy; ARVs = antiretrovirals; BMI = body mass index; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; FDA = Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

References

(See the archived version of Supplement III, February 23, 2009 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, (**http://www.aidsinfo.nih.gov**) for a more complete discussion and reference list.)

General Reviews

1. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr*. 2004;145:439-44.
2. Lee JM, Davis MM, Woolford SJ, Gurney JG. Waist circumference percentile thresholds for identifying adolescents with insulin resistance in clinical practice. *Pediatr Diabetes*. 2009;10:336-42.
3. Carr A and A Carr. Treatment strategies for HIV lipodystrophy. *Current Opinion in HIV & AIDS*. 2007;2(4):332-8.
4. Phillips DR, Hay P et al. Current perspectives on the management and prevention of antiretroviral-associated lipoatrophy. *Journal of Antimicrobial Chemotherapy*. 2008;62(5):866-71.
5. Wohl DA, McComsey G, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clinical Infectious Diseases*. 2006;43(5):645-53

Associated ARVs/Etiology

6. Chang E, Sekhar R, et al. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. *Clinical Infectious Diseases*. 2007;44(11):1509-17.

7. Dube MP, Komarow L, et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nelfinavir or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;45(5):508-14.
8. Haubrich RH, Riddler SA, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009;23(9):1109-18.
9. Hulgan T, Tebas P , et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy [erratum appears in *J Infect Dis*. 2008;Jun 1;197(11):1630.*Journal of Infectious Diseases*. 2008;197(6):858-66.
10. McComseyGA, Libutti DE, et al. Mitochondrial RNA and DNA alterations in HIV lipoatrophy are linked to antiretroviral therapy and not to HIV infection. *Antiviral Therapy*. 2008;13(5):715-22.
11. Tien PC, Benson C, et al. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. *American Journal of Epidemiology*. 2006;163(9):860-9.
12. Van Dyke RB, Wang L, et al. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *Journal of Infectious Diseases*. 2008;198(11):1599-608.
13. Mulligan K, Parker RA, et al. Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2006;41(5):590-7.
14. Scherzer R, Shen W, et al. Comparison of dual-energy X-ray absorptiometry and magnetic resonance imaging-measured adipose tissue depots in HIV-infected and control subjects. *American Journal of Clinical Nutrition*. 2008;88(4):1088-96.

Management

15. Wohl DA, Brown TT. Management of morphologic changes associated with antiretroviral use in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;49(Suppl 2):S93-S100.
16. Carey DL, Baker D, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;46(5):581-9.
17. Cavalcanti RB, Raboud J, et al. A randomized, placebo-controlled trial of rosiglitazone for HIV-related lipoatrophy. *Journal of Infectious Diseases*. 2007;195(12):1754-61.
18. Falutz J, Allas S, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *New England Journal of Medicine*. 2007;357(23):2359-70.
19. Gerschenson M, Kim C, et al. Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen. *Journal of Antimicrobial Chemotherapy*. 2009;63(6):1244-50
20. Hadigan C. and C Hadigan. Peroxisome proliferator-activated receptor gamma agonists and the treatment of HIV-associated lipoatrophy: unraveling the molecular mechanism of their shortcomings [comment]. *Journal of Infectious Diseases*. 2008;198(12):1729-31.
21. Lindegaard B, Hansen T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *Journal of Clinical Endocrinology & Metabolism*. 2008;93(10):3860-9.
22. Lo J, You SM, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA*. 2008;300(5):509-19.
23. Mulligan K, Khatami H, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. *Journal of Clinical Endocrinology & Metabolism*. 2009;94(4):1137-44.

24. Tebas P, Zhang J, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. *Journal of Antimicrobial Chemotherapy*. 2009;63(5):998-1005.

25. Tebas P, Zhang J, et al. Switching to a protease inhibitor-containing, nucleoside-sparing regimen (lopinavir/ritonavir plus efavirenz) increases limb fat but raises serum lipid levels: results of a prospective randomized trial (AIDS clinical trial group 5125s). *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;45(2):193-200.

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (each and in combination)	Onset: 1–20 months after starting therapy (median onset 4 months in one case series). Presentation: • Usually insidious onset of a combination of signs and symptoms: o Generalized fatigue, weakness, and myalgias o Vague abdominal pain, sudden weight loss, unexplained nausea or vomiting o Dyspnea o Peripheral neuropathy. • Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, and respiratory failure).	Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L): • *Adults*: 15%–35% of those receiving NRTI therapy longer than 6 months • *Children*: 29%–32% Symptomatic severe hyperlactatemia (>5.0 mmol/L): • *Adults*: 0.2%–2.5% Symptomatic lactic acidosis/hepatic steatosis: • Rare, but associated with a high fatality rate (33%–57%)	Adult risk factors: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (e.g., d4T, TDF, ribavirin, or tetracycline) • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy	Prevention: • Avoidance of d4T and ddI in combination. • Early recognition of clinical manifestations and adjustment of therapy. Monitoring: • *Asymptomatic*: Measurement of serum lactate is not recommended. • *Clinical signs or symptoms consistent with lactic acidosis*: Obtain blood lactate level*; additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (confirmed with second test): • Consider replacing ddI and d4T with other ARVs. • As alternative, temporarily discontinue all ARVs while conducting additional diagnostic work-up. Lactate >5.0 mmol/L (confirmed with second test)† or >10.0 mmol/L (any one test): • Discontinue all ARVs. • Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). • Anecdotal (unproven) supportive therapies: bicarbonate infusions, tris–hydroxymethyl-aminomethane (THAM), high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C). • Following resolution of

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						clinical and laboratory abnormalities, therapy can be resumed, either with: o an NRTI-sparing regimen; or o a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and o monthly monitoring of lactate for at least 3 months.

* Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a prechilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

† Management may be initiated before the results of the confirmatory test.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARVs = antiretrovirals; BMI = body mass index; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; NRTI = nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate

References

General Reviews

1. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: Report of *12 cases and revie*w of the literature. *Clin Infect Dis*. 2002;34(6): 838-46.
2. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: Comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. 2002;46(3):716-23.
3. Carr A. Lactic acidemia in infection with human immunodeficiency virus. *Clin Infect Dis*. 2003;36(Suppl 2):S96-S100.
4. Fichtenbaum CJ. Metabolic abnormalities associated with HIV infection and antiretroviral therapy. *Curr Infect Dis Rep*. 2009;11(1):84-92.
5. Desai N, Mathur M, Weedon J. Lactate levels in children with HIV/AIDS on highly active antiretroviral therapy. *AIDS*. 2003;17(10):1565-8.
6. Foster C, Lyall H. HIV and mitochondrial toxicity in children. *J Antimicrob Chemother*. 2008;61(1):8-12.

7. Noguera A, Fortuny C, Sanchez E, et al. Hyperlactatemia in human immunodeficiency virus-infected children receiving antiretroviral treatment. *Pediatr Infect Dis J*. 22(9):778-82.

Risk Factors

8. Datta D, Moyle G, Mandalia S, Gazzard B. Matched case-control study to evaluate risk factors for hyperlactataemia in HIV patients on antiretroviral therapy. *HIV Med*. 2003;4(4):311-4.
9. Imhof A, Ledergerber B, Günthard HF, et al. Risk factors for and outcome of hyperlactatemia in HIV-infected persons: Is there a need for routine lactate monitoring? *Clin Infect Dis*. 2005;41(5):721-8.
10. Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS*. 2007;21(18):2455-64.
11. Osler M, Stead D, Rebe K, et al. Risk factors for and clinical characteristics of severe hyperlactataemia in patients receiving antiretroviral therapy: a case-control study. *HIV Med*. 2009;Aug 20.

Monitoring and Management

12. Brinkman K. Management of hyperlactatemia: No need for routine lactate measurements. *AIDS*. 2001;15(6):795-7.
13. Carter RW, Singh J, Archambault C, et al. Severe lactic acidosis in association with reverse transcriptase inhibitors with potential response to l-carnitine in a pediatric HIV-positive patient. *AIDS Patient Care STDs*. 2004;18(3):131-4.
14. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with l-carnitine. *Crit Care Med*. 2003;31(4):1042-7.
15. Delgado J, Harris M, Tesiorowski A, Montaner JS. Symptomatic elevations of lactic acid and their response to treatment manipulation in human immunodeficiency virus-infected persons: A case series. *Clin Infect Dis*. 2001;33(12):2072-4.
16. Lonergan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. *AIDS*. 2003;17(17):2495-9.
17. Mccomsey G, Lonergan JT. Mitochondrial dysfunction: Patient monitoring and toxicity management. *J Acquir Immune Defic Syndr*. 2004;37(Suppl 1):S30-5.
18. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an international AIDS society-USA panel. *J Acquir Immune Defic Syndr*. 2002;31(3):257-75.
19. Wohl DA, Mccomsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006;43(5):645-53.

Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Osteopenia, Osteoporosis, Osteonecrosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and osteoporosis	Following initiation of combination therapy, regardless of regimen. Specific agents of possible concern: TDF, d4T, or PIs.	Onset: Any age; greatest risk in months after initiation of associated ARV Presentation: Most commonly asymptomatic; fracture (rare) Note: Osteoporosis diagnosis in children requires clinical evidence of bone fragility and cannot rely solely on measured low bone density.	Low bone density: 20% of children treated with combination ARV therapy had BMD *z* score <-1.5	• Longer duration of HIV infection • Greater severity of HIV disease • Growth delay, pubertal delay • Low BMI • Lipodystrophy • Nonblack race • Smoking • Steroid use, medroxyprogesterone	Prevention: • Ensure calcium and vitamin D sufficiency. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (smoking, low BMI, steroid use). Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Serum 25-OH-Vitamin D.* • DXA.†	• Ensure calcium and vitamin D sufficiency. • Encourage weight-bearing exercise. • Reduce modifiable risk factors (smoking, low BMI, steroids, medroxyprogesterone). • Role of bisphosphonates not established in children. • Consider change in ARV regimen.
Osteonecrosis	No specific ARV identified. May be related to HIV infection itself.	Onset: Any age Presentation: • Limp; hip or other periarticular pain • Asymptomatic reported in adults	Prevalence: 0.2% in children Incidence: 0.03% per year in children	Children: Unknown Adults: • Steroid use • Alcohol abuse • Hemoglobinopathies • Hyperlipidemia • Pancreatitis • Osteopenia, osteoporosis • Hypercoagulable states	Prevention: Minimize steroid and alcohol use. Monitoring: Consider diagnostic evaluation in patients with unexplained limp, hip or other periarticular pain.	Confirm diagnosis: Plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high. Treatment: • *Early stages*: decreased weight bearing on affected joint and use of analgesic. • *Later stages*: surgical intervention.

*Some experts would periodically measure 25-OH-Vitamin D, especially in HIV-infected urban youth because of high prevalence of vitamin D insufficiency.

† Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with tenofovir.

Key to Abbreviations: ARVs = antiretrovirals; BMI = body mass index; CT = computed tomography; d4T = stavudine; DXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; PIs = protease inhibitors; TDF = tenofovir disoproxil fumarate

References

Osteopenia and Osteoporosis

1. Mora S, Sala N, Bricalli D, et al. Bone mineral loss through increased bone turnover in hiv-infected children treated with highly active antiretroviral therapy. *AIDS*. 2001;15(14):1823-9.
2. Mora S, Zamproni I, Beccio S, et al. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2004;89(1):24-8.
3. Arpadi SM, Horlick M, Thornton J, et al. Bone mineral content is lower in prepubertal HIV-infected children. *J Acquir Immune Defic Syndr*. 2002;29(5):450-4.
4. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. 2005;116(6):e846-54.
5. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: Impact on bone mineral density in HIV-infected children. *Pediatrics*. 2006;118(3):e711-8.
6. Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr*. 2008;152(4):582-4.
7. Jacobson D, Huang J, Shevitz A, et al. Duration of ART and change in bone mineral density over time. 12th Conference on Retroviruses and Opportunistic Infections (Boston). Foundation For Retrovirology and Human Health; 2005; Alexandria, Va. Abstract 825.
8. Jacobson DL, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr*. 2005;41(3):339-46.
9. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: Bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab*. 2007;92(6):2087-99.

Osteonecrosis

10. Gaughan DM, Mofenson LM, Hughes MD, et al. Osteonecrosis of the hip (Legg-Calve-Perthes disease) in human immunodeficiency virus-infected children. *Pediatrics*. 2002;109(5):E74-4.
11. Glesby MJ. Bone disorders in human immunodeficiency virus infection. *Clin Infect Dis*. 2003;37(Suppl 2):S91-5.
12. Morse CG, Mican JM, Jones EC, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. *Clin Infect Dis*. 2007;44(5):739-48.
13. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: Epidemiology, etiologies, and clinical management. *AIDS*. 2003; 17(1), 1-9.

Antiretroviral Treatment Failure in Infants, Children, and Adolescents (Updated August 16, 2010)

OVERVIEW

Panel's Recommendations:

- ***The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay (AI*).***
- ***When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and preserve future antiretroviral options (AII).***
- ***Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy (AII).***
- ***Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist (AI*).***

Although many children can remain on stable antiretroviral therapy for several years *[1-4]*, at some point reassessment of a therapeutic regimen will become necessary. This section will discuss the definitions, causes, assessment, and management of antiretroviral treatment failure and specific issues to consider when changing a drug regimen. Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria. It is important to recognize that not all instances of treatment failure require an immediate change in antiretroviral therapy, and a careful assessment is required to evaluate the etiology of treatment failure and determine the appropriate management strategy.

Although the approach to treatment failure is generally straightforward after failure of the first regimen, it is typically more complex for children who have received more than one antiretroviral regimen. However, with the recent development of new antiretroviral agents, including those directed at new viral targets, the goal of treatment regimens for all patients—whether on initial, second, or subsequent regimen—is complete virologic suppression, combined with the recovery or maintenance of immunologic parameters and improvement in baseline clinical condition (or maintenance of clinical condition if asymptomatic). (See **Assessment of Patients with Antiretroviral Treatment Failure** and **Management of Medication Toxicity or Intolerance**). Decisions regarding changing antiretroviral therapy may need to be individualized and should take into consideration the child's treatment history and toxicities; prior and current detection of drug-resistant virus; current virologic, immunologic, and clinical status; ability to adhere to a new regimen; and available treatment options. In the context of these complexities it is recommended that all children being evaluated for treatment failure be managed in collaboration with a pediatric HIV specialist.

Developmental as well as behavioral characteristics distinguish adolescents from adults and affect decisions around management of treatment failure (see **Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents**). Drug metabolism may vary during puberty, necessitating a reassessment of medication dosing throughout adolescence. In some instances, young adults may require larger doses by weight or by surface area than older adults. In addition, dosing recommendations for adolescents have not been established for a number of new antiretroviral medications now used in adults. Dosing guidance for children and adolescents for all antiretroviral agents can be found in **Appendix B: Pediatric Antiretroviral Drug Information**. The ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*** can provide additional information to help inform management of antiretroviral treatment failure in adolescents.

Definition of Treatment Failure (see Table 12):

Treatment failure is categorized as virologic, immunologic, and clinical failure. Laboratory results must be confirmed with repeat testing before making a final assessment of virologic or immunologic treatment failure.

Virologic Failure: Virologic failure occurs as an incomplete response to therapy or a viral rebound after achieving virologic suppression.

- **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA greater than the level of detection using the most sensitive assay after 12 months of therapy. Children with higher HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.
- **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1,000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound.

Immunologic Failure: Evaluation of immune response in children is complicated by the normal age-related changes in CD4 cell count discussed previously (see **Immunologic Monitoring in Children**). Thus, the normal decline in CD4 values with age needs to be taken into account when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age; absolute CD4 count values in children approach those of adults at about 5 years of age. Consequently, changes in absolute count may be used in children ≥5 years of age.

- **Incomplete immunologic response to therapy:** This is defined as a failure to improve CD4 values by ≥5 percentage points in a child <5 years of age with severe immune suppression (CD4 percentage <15%) or as a failure to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy in a child age 5 years old or older with severe immune suppression (CD4 <200 cells/mm^3).
- **Immunologic decline:** This is defined as a sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age or decline to below pretherapy baseline in absolute CD4 cell count in children who are ≥5 years of age. Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Clinical Failure: The occurrence of new opportunistic infections and/or general clinical disease progression represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation. Clinical findings should be viewed in the context of virologic and immunologic response to therapy; in patients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. For example, development of a new opportunistic infection in a patient who had severe immune suppression at the time of recent initiation of therapy may not reflect failure of virologic suppression, but rather persistence of immune dysfunction despite adequate virologic response. Additionally, immune reconstitution inflammatory syndrome (IRIS) should be excluded as a possible cause of clinical symptoms before it is concluded that there is suboptimal clinical response to therapy. Although clinical events occurring in the first several months after antiretroviral initiation should not necessarily be construed as antiretroviral treatment failure, the occurrence of significant clinical disease progression, such as noted below, requires strong consideration that the current treatment regimen is failing:

- **Progressive neurodevelopmental deterioration:** The presence of two or more of the following findings documented on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.

- **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

Children who experience treatment failure do not always require an immediate change in therapy; careful assessment is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy (see **Assessment of Patients with Antiretroviral Treatment Failure**).

Discordance between Viral, Immune, and Clinical Responses

In general, effective combination antiretroviral therapy that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of new or recurrent HIV-related illnesses. Similarly, ineffective antiretroviral therapy that fails to achieve virologic suppression is commonly accompanied by concordant immunologic and clinical failure *[5]*. However, clinicians may also be presented with patients in whom antiretroviral therapy is associated with failure in one domain (e.g., virologic failure) but a good response in the other domains (e.g., immunologic and clinical response). In fact, the discordance in responses to antiretroviral therapy may occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that antiretroviral treatment failure has truly occurred.

Adequate Clinical and Immunologic Responses despite Incomplete Virologic Response: Some patients who are maintained on combination antiretroviral therapy may maintain immunologic and clinical benefit despite detectable viral replication for up to 3 years *[6-15]*. This observation is the rationale for continuing nonsuppressive antiretroviral therapy for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practicable. The risks and benefits as well as the indications for this approach are discussed in **Approach to the Management of Antiretroviral Treatment Failure** and **Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance**. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are the maintenance of a lower viral load or the selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either “slow-progressors” or “long-term nonprogressors” without therapy.

Poor Immunologic Response despite Virologic Suppression Regardless of Clinical Response: Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. The first considerations in cases of poor immunologic response despite virologic suppression are to exclude laboratory error in CD4 or viral load measurements and to ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count over the first 5–6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see **Diagnosis of HIV Infection in Infants** and **Laboratory Monitoring of Pediatric HIV Infection**). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary.

Additionally, in patients with baseline severe immunosuppression, it is common to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values prior to initiating combination therapy are at higher risk of an impaired CD4 lymphocyte response to antiretroviral therapy and may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression *[3, 12, 16-20]*.

Certain antiretroviral regimens may be associated with a blunted CD4 response. Treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not adjusted downward *[21]*. In adults, antiretroviral regimens containing zidovudine may also impair rise in CD4 count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine; fortunately, this suboptimal CD4 count response to therapy does not seem to confer an increased risk of clinical events *[22]*.

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis) are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in adults without HIV infection *[23]*.

Differential Diagnosis of Poor Immunologic Response despite Virologic Suppression:

Poor Immunologic Response despite Virologic Suppression and Good Clinical Response

- Lab error
- Normal age-related CD4 lymphocyte decline
- Low pretreatment CD4 lymphocyte count or percentage
- Adverse effects of use of zidovudine or the combination of tenofovir + didanosine
- Use of systemic corticosteroids or chemotherapeutic agents
- Conditions that can cause low CD4 values: hepatitis C coinfection, Sjogren's syndrome, tuberculosis, sarcoidosis

Poor Immunologic and Clinical Responses despite Virologic Suppression

- Lab error, including HIV strain/type not detected by VL assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
- Persistent immunodeficiency soon after initiation of antiretroviral therapy but prior to antiretroviral-related reconstitution
- Primary protein-calorie malnutrition
- Untreated tuberculosis
- Malignancy
- Loss of immunologic (CD4) reserve

Poor Clinical Response despite Adequate Virologic and Immunologic Responses: Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunological and virological responses to antiretroviral therapy. Not all cases represent antiretroviral treatment failure. One of the most important reasons for new or recurrent opportunistic conditions despite achieving virologic suppression and immunologic restoration/preservation within the first months of antiretroviral treatment is immune reconstitution inflammatory syndrome (IRIS), which does not represent antiretroviral treatment failure and does not generally require discontinuation of antiretroviral treatment. Children who have suffered irreversible damage to their lungs, brain, or other organs, especially during prolonged and profound pretreatment immunosuppression, may continue to have recurrent infections or symptoms in those damaged organs because the damage may not be reversed by immunologic improvement *[24]*. Such cases do not represent antiretroviral treatment failure and would not be expected to benefit from a change in antiretroviral regimen. Evaluation for and treatment of other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition, and malignancy, should also be undertaken before drawing a conclusion of antiretroviral treatment failure. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jiroveci* pneumonia [PCP] or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason. Such cases may be antiretroviral treatment failure and suggest that improvement in CD4 values may not necessarily represent return of complete immunologic function.

Differential Diagnosis of Poor Clinical Response despite Adequate Virologic and Immunologic Responses:

- IRIS
- Previously unrecognized pre-existing infection or condition (tuberculosis, malignancy)
- Malnutrition
- Clinical manifestations of previous organ damage: brain (strokes, vasculopathy), lungs (bronchiectasis)
- Clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Table 18. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children

Virologic Considerations*	• **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection using the most sensitive assay after 12 months of therapy.† • **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1,000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound.‡
Immunologic Considerations*	• **Incomplete immunologic response to therapy:** Failure in a child <5 years of age with severe immune suppression (CD4 percentage <15%) to improve CD4 values by ≥5 percentage points or failure in a child ≥5 years of age with severe immune suppression (CD4 <200 cells/mm^3) to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy. • **Immunologic decline:** Sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age or decline to below pretherapy baseline in absolute CD4 cell count in children who are ≥5 years of age.§
Clinical Considerations	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction. • **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

* At least two measurements (taken 1 week apart) should be performed before considering a change in therapy.

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5–2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels. Additionally, virologic suppression may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults.

‡ Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., <5,000 copies/mL), especially in children with limited treatment options. The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations and/or nonadherence.

§ Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

References

1. Fraaij PL, Verweel G, van Rossum AM, et al. Sustained viral suppression and immune recovery in HIV type 1-infected children after 4 years of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(4):604-608.
2. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
3. Resino S, Resino R, Micheloud D, et al. Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. *Clin Infect Dis.* 2006;42(6):862-869.
4. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
5. Oliveira R, Krauss M, Essama-Bibi S, et al. HIV viral load predicts World Health Organization (WHO) Stage 3 and 4 events among children in Latin America independent of CD4 level. Paper presented at: (Oral Presentation) 1st International Workshop on HIV Pediatrics; July 16-18 2009; Cape Town, Africa. Abstract O_11.
6. Chiappini E, Galli L, Gabiano C, et al. Early triple therapy vs mono or dual therapy for children with perinatal HIV infection. *JAMA.* 2006;295(6):626-628.
7. Chiappini E, Galli L, Tovo PA, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS.* 2006;20(2):207-215.
8. de Martino M, Galli L, Moriondo M, et al. Dissociation of responses to highly active antiretroviral therapy: Notwithstanding virologic failure and virus drug resistance, both CD4+ and CD8+ T lymphocytes recover in HIV-1 perinatally infected children. *J Acquir Immune Defic Syndr.* 2001;26(2):196-197.
9. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
10. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
11. Kovacs A, Montepiedra G, Carey V, et al. Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response. *J Infect Dis.* 2005;192(2):296-302.
12. Nikolic-Djokic D, Essajee S, Rigaud M, et al. Immunoreconstitution in children receiving highly active antiretroviral therapy depends on the CD4 cell percentage at baseline. *J Infect Dis.* 2002;185(3):290-298.
13. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
14. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.
15. Sufka SA, Ferrari G, Gryszowka VE, et al. Prolonged CD4+ cell/virus load discordance during treatment with protease inhibitor-based highly active antiretroviral therapy: immune response and viral control. *J Infect Dis.* 2003;187(7):1027-1037.
16. Moore DM, Hogg RS, Chan K, et al. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. *AIDS.* 2006;20(3):371-377.
17. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis.* 2007;44(3):441-446.
18. Newell ML, Patel D, Goetghebuer T, et al. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis.* 2006;193(7):954-962.
19. Resino S, Alvaro-Meca A, de Jose MI, et al. Low immunologic response to highly active antiretroviral therapy in naive vertically human immunodeficiency virus type 1-infected children with severe immunodeficiency. *Pediatr Infect Dis J.* 2006;25(4):365-368.
20. Soh CH, Oleske JM, Brady MT, et al. Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet.* 2003;362(9401):2045-2051.
21. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis.* 2005;41(6):901-905.
22. Huttner AC, Kaufmann GR, Battegay M, et al. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS.* 2007;21(8):939-946.

23. Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force. *N Engl J Med.* 1993;328(6):373-379.
24. Graham SM. Non-tuberculosis opportunistic infections and other lung diseases in HIV-infected infants and children. *Int J Tuberc Lung Dis.* 2005;9(6):592-602.

ASSESSMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE

Panel's Recommendations:

- ***Assess adherence to therapy and barriers and interventions to improve adherence because inadequate adherence is the most common cause of antiretroviral treatment failure (AII).***
- ***Assess medication intolerance (AIII).***
- ***Assess issues related to pharmacokinetics because developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral drug exposure that results in antiretroviral treatment failure (AII).***
- ***Perform antiretroviral drug-resistance testing when virologic failure occurs and prior to changing to a new regimen (AI*).***
- ***Perform assessment in collaboration with a pediatric HIV specialist (AI*).***

Each patient with an incomplete response to therapy should be assessed to determine the cause of treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. The assessment of a child with suspicion of treatment failure should include evaluation of adherence to therapy; medication intolerance; issues related to pharmacokinetics that could result in low drug levels or elevated, potentially toxic levels; and evaluation of suspected drug resistance. The main challenge to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with the subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the antiretroviral regimen.

Table 13 outlines a comprehensive approach to evaluating causes of treatment failure in children, with particular attention to adherence. An extensive history should focus on the details of drug administration as well as changes in the social and psychological circumstances of the family likely to impact the child's ability to adhere to therapy. In some situations, it may be necessary to directly observe drug-taking behaviors either in the clinic, at home, or within the hospital because history alone may not fully identify the barriers to complete adherence *[1-2]*.

Adherence Issues (For more details, see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents** and **Table 11**.)

When treatment failure is observed, clinicians need to assess the likely contribution of adherence problems to the failure of the current regimen. In patients on initial therapy, poor virologic response or widely fluctuating viral loads are commonly an indication of poor adherence, particularly in the presence of susceptible virus. Even small lapses in adherence can lead to antiretroviral treatment failure *[3-7]*. Although adherence should be addressed at each medical visit for all children receiving antiretroviral therapy, suspicion of treatment failure warrants increased scrutiny. Patterns of adherence can change over time and may be influenced by a large number of factors related to the drugs themselves as well social and psychological issues of the child and the family.

Evaluation of whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects is important for determining what changes would be best suited to the individual requirements of the child and family. Intensive family education, training in the administration of prescribed medications, and discussion of the importance of adherence to the drug regimen should be reinforced. If competing family needs are identified as impediments to adherence, social issues may need to be addressed before adherence can be improved. Issues to be addressed may include achieving financial or housing security, assessing concomitant mental health problems, accessing substance abuse treatment, and

initiating a discussion around HIV disclosure. In some situations, clinicians may need to involve outside agencies such as child protective services to ensure support of the child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting the child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and family to improve adherence to the current or new regimen. Directly observed therapy (DOT) may be used to identify additional factors impeding adherence as well as to confirm drug administration.

Pharmacokinetic Issues

In addition to poor adherence, inadequate drug exposure can result in treatment failure *[8]*. Children consistently require higher weight-based dosing of antiretroviral drugs compared with adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range *[9]*. Causes of subtherapeutic drug levels may include failure to increase dosing for rapid growth of the child or impaired absorption because of gastrointestinal symptoms, such as vomiting or diarrhea. Drug exposure may be enhanced or reduced by administering medications with food; the clinician should review the food/fasting requirements of the regimen with the patient and caregiver. Drug interactions can alter drug metabolism; all concomitant medications, including over-the-counter medications and nutritional and herbal supplements, should be reviewed to evaluate whether they may be contributing to poor treatment response. (See the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.) Several recent studies suggest that genetic polymorphisms may influence pharmacokinetics and therapeutic response for a number of antiretroviral medications *[10-11]*. In some circumstances, therapeutic drug monitoring can be considered for children receiving selected drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

Suspected Drug-Resistance Issues (See **Antiretroviral Drug-Resistance Testing**.)

Antiretroviral drug resistance may develop in children with inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs of the current regimen, it is unlikely that the child is taking these medications. The presence of mutations supports inadequate drug exposure and failure to fully suppress viral replication. Antiretroviral resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of its discontinuation. In the absence of the selective pressure of antiretroviral drugs, virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays. Resistance testing can be used to guide current management as well as to identify active antiretroviral medications for future regimens. Other laboratory tests such as tropism assays may be indicated as well if CCR5 inhibitors are being considered for treatment in the subsequent regimen.

Table 19. Assessment of Antiretroviral Treatment Failure

Assessment	Method	Intervention
Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Get description of: o *WHO* gives medication o *WHAT* is given (names, doses) o *WHERE* medications are kept, administered o *WHEN* they are taken/given • Have open-ended discussion of experiences taking/giving medications and barriers/challenges 2. Review pharmacy records • Assess timeliness of refills 3. Observe medication administration • Observe dosing/administration in clinic • Conduct home-based observation by visiting health professional • Admit to hospital for trial of therapy o Observe administration/tolerance o Monitor treatment response 4. Conduct psychosocial assessment • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes: o Status of caregiver, financial stability, housing, intimate relationships o School and achievement o Substance abuse (child, caretaker, family members) o Mental health and behavior o Child/youth and caretaker beliefs about antiretroviral therapy o Disclosure status (to child and others)	Identify or re-engage family members to support/supervise adherence. Establish fixed daily times and routines for medication administration. Avoid confusion with drug names by explaining that drug therapies have generic names and trade names, and many agents are coformulated under a third or fourth name. Explore opportunities for facility or home-based directly observed therapy. Simplify medication regimen if feasible. Substitute new agents if single ARV is poorly tolerated. Consider gastric tube placement to facilitate adherence. Consider directly observed therapy (DOT). Use tools to simplify administration (pill boxes, reminders including alarms, integrated medication packaging for AM or PM dosing, others). Suggest relaxation techniques. Address competing needs through appropriate social services. Address and treat concomitant mental illness and behavioral disorders. Initiate disclosure discussions with family/child. Consider need for child protection services and alternate care settings when necessary.
Pharmaco-kinetics and Dosing	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific antiretroviral drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).	Adjust drug doses. Discontinue or substitute competing medications. Reinforce applicable food restrictions.
Resistance Testing	1. Perform genotypic and phenotypic resistance assays (see **Antiretroviral Drug-Resistance Testing**). 2. Perform tropism assay, as appropriate.	

References

1. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(7):716-718.
2. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. *AIDS Patient Care STDS.* 2006;20(4):275-284.
3. Gibb DM, Goodall RL, Giacomet V, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J.* 2003;22(1):56-62.
4. Katko E, Johnson GM, Fowler SL, et al. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(12):1174-1176.
5. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics.* 2002;109(4):e61.
6. van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(8):743-747.
7. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 1999;18(8):682-689.
8. Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ.* 2006;332(7551):1183-1187.
9. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.
10. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr.* 2007;45(3):280-285.
11. Saitoh A, Sarles E, Capparelli E, et al. CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. *AIDS.* 2007;21(16):2191-2199.

APPROACH TO THE MANAGEMENT OF ANTIRETROVIRAL TREATMENT FAILURE

Panel Recommendations:

- ***The causes of treatment failure, which include drug resistance, poor absorption of medications, poor adherence, inadequate dosing, and drug-drug interactions, should be assessed and addressed (AII).***
- ***When deciding how to treat a child with treatment failure, the probability of achieving durable suppression based on the prior treatment history, drug resistance, drug potency, and likelihood of adherence should be considered as well as the future options available should durable suppression not be achieved; in addition, the future availability and timing of novel agents should be considered (AII).***
- ***Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist (AI*).***

General

Once the causes of failure have been identified and addressed, the child should be assessed to determine whether a change in the antiretroviral regimen is necessary. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The immediacy of implementing a more effective treatment regimen depends on the immunologic status of the child, with the greatest urgency for patients with clinical disease progression or clinical failure. The likelihood of achieving and maintaining undetectable plasma viral load depends on the extent of drug resistance, the number and quality of available agents that are active against the child's virus, and the likelihood of adherence to the new regimen.

Timing of Initiation of a New Regimen: Relative Importance of Virologic Suppression and Immunologic Improvement

Because immunologic improvement typically results from achieving undetectable plasma viral load *[1]*, the urgency of re-establishing virologic suppression depends on the clinical and immunologic status of a child. For example, for older children or adolescents with very low CD4 cell counts (e.g., <200 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline or clinical disease progression and is strongly recommended. A patient with less immunosuppression may not be at significant risk of clinical disease progression in the near future, so an immediate change in therapy is less urgent. However, continued treatment of a child with persistently detectable viremia increases the risk of immunologic or clinical disease progression and leads to further accumulation of resistance mutations, possibly further limiting future treatment options *[2]*.

Likelihood of Viral Suppression below the Limit of Detection Using the Most Sensitive Assay

When deciding whether to change a child's antiretroviral regimen, a clinician must assess whether such a change is likely to achieve significantly better virologic control than the current regimen. Although complete virologic suppression should be the goal, this may not always be achievable in HIV-infected children. Clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels *[1]*. However, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring mutations associated with resistance. Anticipating and minimizing toxicities is central to the clinician-patient discussion. The likelihood of adherence to a new regimen plays a significant role in determining whether to change an antiretroviral regimen; if a child is unlikely to adhere to a new regimen, resistance will develop and sustainable virologic suppression will not be achieved. Although studies differ on the exact predictors of adherence, several contributing factors have been noted. These include medication characteristics *[3]*, psychosocial stressors *[4-5]*, health beliefs *[6]*, and prior adherence to medication (see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents** for more detail). Importantly, the pediatric patient's adherence to antiretroviral therapy may change over time as the child moves through progressive developmental stages, and any changes in these risk factors can occur rapidly and unexpectedly. Thus, a clinician may choose to target a new antiretroviral regimen to start at a time when the child is most likely to adhere to this regimen for a sustained period.

Categories of Children with Treatment Failure and Approaches to Consider

No Viral Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications suggests that the virus is not being exposed to the antiretroviral agents. This lack of antiretroviral drug exposure is usually due to nonadherence, but it is important to exclude other factors such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be assured, then resuming the existing current regimen should result in undetectable plasma levels. Resistance testing should take place while the child is on therapy, because predominant plasma viral strains may quickly revert to wild-type and fail to reveal the drug-resistant virus that would have been detectable while the patient was receiving therapy (see **Antiretroviral Drug-Resistance Testing**). Thus, if a child with prior therapy develops resistant virus and then stops therapy, sensitive virus will dominate in the absence of therapy. In this situation, resuming the prior therapy would fail to suppress the virus because the resistant virus would again emerge. An approach to identify resistance in this situation is to restart the prior medications while emphasizing adherence and repeating the resistance testing in 4 weeks (unless undetectable plasma viral load has already been achieved). If plasma virus is undetectable by ultrasensitive assays, it is likely that the virus is susceptible to the current therapy.

Viral Resistance to Current Therapy

The goal in this situation is to start a new regimen in order to fully suppress and sustain plasma viral load below the limits of detection and prevent the emergence of virus with additional resistance mutations. This requires a regimen that includes at least two, and preferably three, fully active agents. The choice of new agents should be based on current and past resistance testing (see **Antiretroviral Drug-Resistance Testing**), the antiretroviral history, availability of new drugs and classes of agents, and consideration of potential toxicities. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for cross resistance of some drugs within a single class, substituting a new drug from the same previously used class does not assure that the replacement drug will be fully active. This is particularly true for the NNRTIs nevirapine and efavirenz, for which cross resistance with drug mutations is uniformly seen.

The availability of multiple new antiretroviral drugs, including some with new viral targets, makes complete virologic suppression achievable for many adult patients with treatment failure. Unfortunately, the lack of pediatric formulations and dosing information for many of these agents limits the number of options available for children. Thus, it remains difficult to identify a new, active regimen for many children with extensive prior therapy. (See **The Use of Antiretroviral Agents Not Approved for Use in Children**.)

If there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen would also be difficult, the emphasis and effort should be placed on addressing barriers to adherence. In such cases, some clinicians may choose to continue a nonsuppressive regimen that may provide some clinical and immunologic benefit while preserving future antiretroviral choices (see **Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance**). Treating with the same nonsuppressive regimen in such situations should be regarded as an acceptable but not ideal short-term strategy. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

Extensive Drug Resistance Such That Two Fully Active Agents cannot be Identified or Administered

In the case of children for whom undetectable plasma virus is not achievable because two or more fully active agents cannot be identified, the goal is to preserve immunologic function and prevent clinical disease progression while preserving future options for new agents that are not yet available. Adult cohort studies suggest that there may be ongoing immunologic and clinical benefit if the HIV viral load can be maintained lower than 10,000–20,000 copies/mL *[7-8]*. Several cohort studies show a clinical benefit of remaining on antiretroviral therapy whether this leads to a decrease in the viral load. The principal risk associated with continuing a failing regimen is the development of additional resistance mutations that can limit future treatment options. Interrupting therapy completely, on the other hand, may cause a rapid increase in viral load, a decrease in CD4 cell count that is frequently persistent, and an increased risk of clinical disease progression *[4]*. This approach should only be considered in special circumstances when there is a low risk that therapy interruption will quickly lead to severe immunosuppression (i.e., CD4 values at the time of therapy interruption are high). The goal of continued treatment with an incompletely suppressive regimen is to select for resistant virus with reduced viral fitness that will cause slower disease progression while reducing the risk of drug toxicity and the development of new resistance mutations to multiple classes of drugs. The overall goal of these alternative strategies is to prevent clinical and immunological progression until additional active drugs are available that can be used to design a regimen that is expected to achieve undetectable plasma viral load *[1, 9-17]*. This approach should be regarded as acceptable but not ideal, these patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

When managing disease progression in a patient with advanced disease and extensive resistance, the patient's quality of life must be considered. The relative benefits (e.g., reduced viral fitness, continued clinical benefit

despite resistance, etc.) and burdens of continuing a failing antiretroviral regimen should be discussed. Decisions to continue, discontinue, or simplify antiretroviral therapy should be made collaboratively with patients, families, and clinicians and should be consistent with the patients'/families' stated values and goals for care.

References

1. Kovacs A, Montepiedra G, Carey V, et al. Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response. *J Infect Dis.* 2005;192(2):296-302.
2. Eshleman SH, Krogstad P, Jackson JB, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). *J Infect Dis.* 2001;183(12):1732-1738.
3. Boni S, Pontali E, De Gol P, et al. Compliance to combination antiretroviral therapy in HIV-1 infected children. *Int J Antimicrob Agents.* 2000;16(3):371-372.
4. Gibb DM, Duong T, Leclezio VA, et al. Immunologic changes during unplanned treatment interruptions of highly active antiretroviral therapy in children with human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J.* 2004;23(5):446-450.
5. Mellins CA, Brackis-Cott E, Dolezal C, et al. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(11):1035-1041.
6. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2000;19(12):1148-1153.
7. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet.* 2004;364(9428):51-62.
8. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr.* 2004;37(1):1147-1154.
9. Abadi J, Sprecher E, Rosenberg MG, et al. Partial treatment interruption of protease inhibitor-based highly active antiretroviral therapy regimens in HIV-infected children. *J Acquir Immune Defic Syndr.* 2006;41(3):298-303.
10. de Martino M, Galli L, Moriondo M, et al. Dissociation of responses to highly active antiretroviral therapy: Notwithstanding virologic failure and virus drug resistance, both CD4+ and CD8+ T lymphocytes recover in HIV-1 perinatally infected children. *J Acquir Immune Defic Syndr.* 2001;26(2):196-197.
11. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
12. Deeks SG, Martin JN, Sinclair E, et al. Strong cell-mediated immune responses are associated with the maintenance of low-level viremia in antiretroviral-treated individuals with drug-resistant human immunodeficiency virus type 1. *J Infect Dis.* 2004;189(2):312-321.
13. Devereux HL, Emery VC, Johnson MA, et al. Replicative fitness in vivo of HIV-1 variants with multiple drug resistance-associated mutations. *J Med Virol.* 2001;65(2):218-224.
14. Eron JJ, Jr., Bartlett JA, Santana JL, et al. Persistent antiretroviral activity of nucleoside analogues after prolonged zidovudine and lamivudine therapy as demonstrated by rapid loss of activity after discontinuation. *J Acquir Immune Defic Syndr.* 2004;37(5):1581-1583.
15. Nikolic-Djokic D, Essajee S, Rigaud M, et al. Immunoreconstitution in children receiving highly active antiretroviral therapy depends on the CD4 cell percentage at baseline. *J Infect Dis.* 2002;185(3):290-298.
16. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
17. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.

CHOICE OF NEXT ANTIRETROVIRAL REGIMEN FOR TREATMENT FAILURE WITH EVIDENCE OF DRUG RESISTANCE

Panel's Recommendations:

- ***Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing, including past and current resistance test results (AI*).***
- ***Ideally, use three fully active antiretroviral medications in the new regimen, assessing anticipated antiretroviral activity based on past treatment history and resistance test results (AII*).***
- ***Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist (AI*).***
- ***Use of novel agents with limited available pharmacokinetic and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist (AIII).***

General

After carefully reaching a decision that a change in therapy is needed, the clinician should attempt to identify at least two but preferably three fully active antiretroviral agents on the basis of resistance testing, prior antiretroviral exposure, acceptability to the patient, and likely adherence *[1-5]*. This often requires the use of one or more new drug classes. Substitution or addition of a single drug to a failing regimen should be avoided because this approach is unlikely to achieve and sustain an undetectable plasma viral load and frequently will result in additional drug resistance. A drug may be "new" to the patient but have diminished antiviral potency due to the presence of drug mutations that confer cross resistance within a drug class. In children who are changing therapy due to occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher levels within the central nervous system *[6-9]*.

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient in an age- and development-appropriate manner and with the patient's caregivers. The clinician must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate coordination of a regimen. Timing of medication administration is particularly important to ensure adequate antiretroviral drug exposures throughout the day. Palatability, pill size, pill number, and dosing frequency all need to be considered when choosing a new regimen.

Choice of Therapy with Viral Resistance to Current Therapy: Goal of Complete Virologic Suppression

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made in collaboration with a pediatric HIV specialist. Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug potency in the new regimen. A general strategy for regimen change is shown in **Table 14**, although as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child has received initial therapy with an NNRTI-based regimen, a change to a PI-based regimen is recommended; if a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross resistance to the NNRTI efavirenz and vice versa; however, the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus in the presence of a limited number of NNRTI resistance-associated mutations. Etravirine is currently approved for use only in adults; pediatric studies are under way.

Choice of the new dual-NRTI component is particularly important when constructing a regimen because the choice of an insufficiently potent NRTI may result in the selection of additional NRTI-related drug mutations.

Resistance testing is essential to properly select a potent NRTI combination, and interpretation of these results should take place in collaboration with an expert in pediatric HIV infection (see **Antiretroviral Drug-Resistance Testing**). In this case, use of a triple-class regimen or a novel agent may be necessary.

If a patient has substantial pre-existing resistance or if the initial regimen contained drugs from all three major classes (NRTI, NNRTI, and PI), the drug-resistance profile and management approach is likely to resemble that of a patient who has had multiple antiretroviral regimen failures (see **Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered**). In this situation, a new regimen with only two fully active agents may be the best available option. Lopinavir/ritonavir-based regimens have shown durable antiretroviral activity in antiretroviral treatment-experienced children, including children with prior PI therapy *[10-12]*. Adult studies of treatment-experienced patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), possibly coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced, multiresistant patients is associated with better virologic responses *[13-14]*. **Appendix B: Pediatric Antiretroviral Drug Information** provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity as well as discussion of available pediatric data for the approved antiretroviral drugs, including new drugs in existing classes such as darunavir and new classes of drugs such as CCR5 antagonists and integrase inhibitors. Maraviroc (CCR5 inhibitor) and raltegravir (integrase inhibitor) are approved for use in adolescents 16 years or older and can be considered for management of older adolescents with multidrug failure; pediatric trials are under way or in development.

Previously prescribed drugs discontinued due to poor tolerance or poor adherence may sometimes be reintroduced. Reintroduction of the drugs is particularly possible if antiretroviral resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to pill formulation). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir *[15-17]*. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children might be justified and is ideally done in the framework of a clinical trial (see **The Use of Antiretroviral Agents Not Approved for Use in Children**). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

The HIV entry inhibitor enfuvirtide (T-20) has been approved for use in heavily treatment experienced patients based on potent antiretroviral activity in heavily treatment experienced adults and has been approved for use in children age ≥6 years *[18-19]*. Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children ≥6 years of age; this therapy has the disadvantage of administration by subcutaneous injection twice daily *[20-21]*. Enfuvirtide adherence in adolescent populations remains a unique challenge when compared with younger children. However, this agent should be considered as an option when designing a new regimen for pediatric populations who have failed treatment with multiple classes of antiretroviral medications.

Pharmacokinetic studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that pharmacokinetic targets for both PIs can be achieved or exceeded when used in combination in adults *[22-24]* and in children *[25-27]*. Pharmacokinetic studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs *[28-29]*. A study in Thailand of 50 PI-naïve but NRTI+/-NNRTI experienced children treated with a combination of lopinavir/ritonavir (230/57.5 mg/m^2 twice daily) and saquinavir (50 mg/kg twice daily, maximum dose 1,000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks for ≥50% of patients. The regimen was well tolerated but hyperlipidemia was common. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series *[30]* but should be used cautiously due to its complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring (TDM) may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity

due to the presence of drug-resistance mutations (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

When searching for at least two fully active agents in cases of extensive drug resistance, the clinician should consider the potential availability and future use of newer therapeutic agents that may not be studied or approved in children or may be in clinical development (see **The Use of Antiretroviral Agents Not Approved for Use in Children**). Information concerning potential clinical trials can be found at **http://aidsinfo.nih.gov/clinical_trials** and through collaboration with a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered

The creation of an effective and sustainable therapeutic regimen may not be possible with currently available agents due to lack of potency in the face of extensive drug resistance or the patient's inability to adhere to or tolerate combination antiretroviral therapy. In such cases, nonsuppressive regimens (or "holding regimens") are sometimes used with the overall objective of preventing clinical and immunological deterioration pending availability of additional active drugs that can be used to design a regimen that is expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, there can be immunologic and clinical benefit despite persistent viremia when patients are treated with lamivudine monotherapy or when they are treated with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir *[31-32]*.

Because the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus in the presence of a limited number of NNRTI resistance-associated mutations, efavirenz or nevirapine should not be continued as part of a failing regimen if NNRTI resistance is documented.

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low *[33-35]*. However, continued PI use, in the presence of resistance, may limit viral replication and be beneficial to some patients.

In general, every effort should be made to avoid adding a single, new, fully active agent to these "holding" nonsuppressive regimens because such use of a single fully active agent will quickly lead to diminished activity of that agent. When clinical or immunologic deterioration occurs in such cases, it is often appropriate to use investigational agents or agents approved for older age groups as a second fully active drug in the new regimen (see **The Use of Antiretroviral Agents Not Approved for Use in Children**).

Table 20. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression*

Prior Regimen	Recommended Change
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI
2 NRTIs + PI	• 2 NRTIs (based on resistance testing) + NNRTI • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir boosting, based on resistance testing) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir boosting, based on resistance testing)
3 NRTIs	• 2 NRTIs (based on resistance testing) + (NNRTI *or* PI) • NRTI(s) (based on resistance testing) + (NNRTI + PI)
Failed regimens including NRTI, NNRTI, PI	• >1 NRTI (based on resistance testing) + a newer PI (with low-dose ritonavir boosting, based on resistance testing) • >1 NRTI + dual-boosted PI (LPV/r + SQV, LPV/r + ATV) (consider adding either one or more of T-20, ETR, or an integrase inhibitor) • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + ETR • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + T-20 and/or CCR5 antagonist and/or integrase inhibitor • If patient refuses PI and/or ritonavir boosting: NRTI(s) + T-20 and/or integrase inhibitor and/or CCR5 antagonist

* Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression.

Key to Abbreviations: T-20 = enfuvirtide, ATV = atazanavir, ETR = etravirine, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SQV = saquinavir

References

1. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS.* 2009;23(17):2289-2300.
2. Steigbigel RT, Cooper DA, Teppler H, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis.* 2010;50(4):605-612.
3. De Luca A, Di Giambenedetto S, Cingolani A, et al. Three-year clinical outcomes of resistance genotyping and expert advice: extended follow-up of the Argenta trial. *Antivir Ther.* 2006;11(3):321-327.
4. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 2000;14(9):F83-93.
5. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.* 2002;16(2):209-218.
6. Antinori A, Giancola ML, Grisetti S, et al. Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS.* 2002;16(14):1867-1876.
7. Antinori A, Perno CF, Giancola ML, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: different patterns of phenotypic resistance in CSF and plasma. *Clin Infect Dis.* 2005;41(12):1787-1793.
8. Capparelli EV, Letendre SL, Ellis RJ, et al. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother.* 2005;49(6):2504-2506.
9. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol.* 2008;65(1):65-70.
10. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS.* 2004;18(2):247-255.
11. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J.* 2005;24(10):867-873.
12. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
14. Temesgen Z, Cainelli F, Poeschla EM, et al. Approach to salvage antiretroviral therapy in heavily antiretroviral-experienced HIV-positive adults. *Lancet Infect Dis.* 2006;6(8):496-507.
15. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis.* 2005;41(2):236-242.
16. Nijhuis M, Schuurman R, de Jong D, et al. Lamivudine-resistant human immunodeficiency virus type 1 variants (184V) require multiple amino acid changes to become co-resistant to zidovudine in vivo. *J Infect Dis.* 1997;176(2):398-405.
17. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004;18(12):1691-1696.
18. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2002;21(7):653-659.
19. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2004;23(8):713-718.
20. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J.* 2007;26(9):799-805.
21. Zhang X, Lin T, Bertasso A, et al. Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol.* 2007;47(4):510-517.
22. Ribera E, Azuaje C, Lopez RM, et al. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. *AIDS.* 2006;20(8):1131-1139.
23. Stephan C, von Hentig N, Kourbeti I, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/ritonavir. *AIDS.* 2004;18(3):503-508.

24. van der Lugt J, Autar RS, Ubolyam S, et al. Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naive HIV-1-infected adults. *J Antimicrob Chemother.* 2008;61(5):1145-1153.
25. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
26. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
27. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
28. Collier AC, Tierney C, Downey GF, et al. Randomized study of dual versus single ritonavir-enhanced protease inhibitors for protease inhibitor-experienced patients with HIV. *HIV Clin Trials.* 2008;9(2):91-102.
29. Walmsley SL, Katlama C, Lazzarin A, et al. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). *J Acquir Immune Defic Syndr.* 2008;47(4):429-440.
30. King JR, Acosta EP, Chadwick E, et al. Evaluation of multiple drug therapy in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2003;22(3):239-244.
31. Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). *AIDS.* 2006;20(6):795-803.
32. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis.* 2005;192(9):1537-1544.
33. Garcia-Gasco P, Maida I, Blanco F, et al. Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. *J Antimicrob Chemother.* 2008;61(3):699-704.
34. Napravnik S, Edwards D, Stewart P, et al. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. *J Acquir Immune Defic Syndr.* 2005;40(1):34-40.
35. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA.* 2005;293(7):817-829.

THE USE OF ANTIRETROVIRAL AGENTS NOT APPROVED FOR USE IN CHILDREN

Panel's Recommendations:

- ***Some children with HIV need to use antiretrovirals that are not yet approved for their age range because many of the recently approved, more convenient, and potent agents are approved for adults before pharmacokinetic, safety, and efficacy data are available in children (AII).***
- ***This "off-label" use of antiretrovirals can be risky because dosing recommendations have not yet been made and often cannot be inferred from a simple calculation using the adult dose and the child's weight (AII).***
- ***Off-label use of antiretrovirals should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and pharmacokinetics of these agents (AI*).***
- ***Whenever possible, use of antiretrovirals that are not yet FDA approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval (AIII).***

It has long been practice for physicians, especially pediatricians, to prescribe medications in "off-label" situations, meaning for indications or populations that do not fall within the FDA's official indication *[1]*. The relatively small market for pediatric antiretroviral drugs and few children available for clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some antiretroviral drugs at the same time they are approved in adults. Pediatric HIV specialists may need to prescribe these agents because of

high levels of resistance seen in heavily treated children and adolescents and improvements in tolerability and ease of adherence with newer agents with less frequent dosing.

One distinct advantage of some of the newer medications is improved tolerability. Examples include a reduction in the number or severity of side effects with newer PIs and the ability to create simpler regimens using fixed-dose combination tablets or once-daily preparations. The incentive to use these drugs in such instances is that these regimens will lead to improved adherence and thus better long-term outcomes.

Another major factor leading to the off-label use of antiretrovirals has been the development of new drugs belonging to novel classes of agents effective against resistant virus. In the United States, many older perinatally infected children have extensive drug resistance resulting from incomplete viral suppression due to treatment with multiple nonsuppressive regimens. Cross resistance between fully approved antiretrovirals within a class complicates finding an array of agents likely to fully suppress the virus. In an effort to find a regimen likely to achieve complete virologic suppression in an individual patient, providers must find at least two and preferably three drugs with demonstrated activity against the patient's virus. Success is almost impossible in heavily treatment experienced children using only drugs with approved pediatric label indications; thus providers may use drugs not yet approved for children in order to provide optimal virologic response. The recent FDA approvals for adults of raltegravir and maraviroc (the first integrase inhibitor and CCR5 inhibitor, respectively) have provided new options for therapy to achieve virologic suppression in patients experiencing treatment failure with extensive antiretroviral resistance.

However, the use of agents not yet approved for pediatric use causes some difficulties, and one of the major issues is lack of data on appropriate dosing in children. Agents are approved for adult use prior to pediatric use because safety and pharmacokinetic studies in children have not yet been completed. Sometimes these studies are ongoing and some data are available, but other times these studies have not yet begun. It is essential for providers prescribing agents for off-label use to consult with pediatric HIV experts to avail themselves of the latest information from ongoing studies.

The possibility of age-related side effects is another concern when initiating off-label antiretroviral use. To date no antiretroviral has been found to have adverse effects that uniquely preclude use in children, but until an agent has been tested in children it cannot be considered to be free of such an effect. Additionally, adverse effects noted in adults may be of more substantial concern in the growing and developing child.

Even more difficult than the potential for adverse effects has been the difficulty of dosing of antiretrovirals in pediatric patients. As absorption, hepatic metabolism and excretion change with age, so will drug levels change in children *[2]*. The difficulty in dosing children as they increase in weight is exacerbated by changing pharmacokinetics. The direct extrapolation of the adult dose to a pediatric dose, based either on body weight or body surface area, has been shown in clinical trials of several antiretroviral agents to underestimate the appropriate pediatric dose *[3]*.

In summary, the use of antiretroviral agents without a pediatric indication is an absolute necessity for the treatment of some children with HIV, but it must be done with care. **It is essential that the provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.**

References

1. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J*. 2009;28(3):204-209.
2. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167.
3. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. 2008;83(2):300-306.

ROLE OF THERAPEUTIC DRUG MONITORING IN MANAGEMENT OF TREATMENT FAILURE

Therapeutic drug monitoring (TDM) is the use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in antiretroviral treatment because *[1]*:

- There is high interpatient variability in antiretroviral exposure (plasma drug concentrations) using standard recommended doses;
- Low drug exposure can lead to suboptimal virologic response to therapy; and
- High plasma concentrations can be associated with increased risk of drug toxicity.

Developmental pharmacokinetic differences contribute to greater variability and a greater frequency of suboptimal antiretroviral exposure in pediatric patients than in adults *[2]*. Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated antiretroviral drug dose. Even when using dose recommendations from published pediatric guidelines, children frequently receive inadequate antiretroviral doses *[3]*.

There are two main situations in which TDM might be useful in a child who is failing therapy. First, TDM can be used to rule out subtherapeutic drug levels as a cause of failure. Such inadequate drug levels could result from malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance. Second, drug levels can be used to optimize the dose of a drug when changing to a new regimen in a patient whose virus has a reduced susceptibility to that drug.

For TDM to be useful there needs to be a clearly defined relationship between antiretroviral concentrations and anti-HIV effects *[4-6]*. This association is strongest with PI and NNRTI drugs *[7]*, but maintaining adequate NRTI serum concentrations has also been shown to be important for maximal anti-HIV activity *[8]*. The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents *[6]*. Concentration-response relationships have been established with minimum plasma concentrations (C_{min} or C_{trough}) or area under the curve (AUC), but the optimal measure is not defined for all antiretroviral drugs *[9]*.

Table 15 presents recommendations for the minimum target trough concentrations of PIs and NNRTIs in patients with wild-type virus. In antiretroviral-experienced patients, the choice of minimum target trough concentration should be based on results of resistance testing *[10-12]*. Although it is intrinsically difficult to demonstrate benefit of TDM using double-blind studies, limited data suggest targeted concentrations can be achieved with TDM, clinical responses can be improved with increased or modified doses, and TDM information can be helpful in decision making *[7, 13-17]*. The clinician should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

TDM is not recommended for routine use but may be considered in the following circumstances in which it is potentially useful:

- Patients in whom clinical response is different from that expected;

- Treatment-experienced patients infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful;
- Patients with potential drug administration difficulties, including suboptimal dietary intake, malabsorption, incorrect dose, caregiver measuring errors, or adherence concerns; and
- Patients who experience drug or food interactions, including alteration of drug formulations by crushing or mixing with various foods and liquids.

Current limitations for pediatric antiretroviral TDM include:

- Prolonged time for laboratory processing in the face of potentially diminishing benefit the longer the patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results *[18-19]*;
- Single trough measurements within the target range do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third party reimbursement of costs associated with TDM.

Table 21. Suggested Minimum Target Trough Concentrations*

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir (Measurable active [M8] metabolite)	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

* Reprinted from: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. **http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf**.

References

1. Fraaij PL, Rakhmanina N, Burger DM, et al. Therapeutic drug monitoring in children with HIV/AIDS. *Ther Drug Monit.* 2004;26(2):122-126.
2. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.
3. Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ.* 2006;332(7551):1183-1187.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834.
5. Anderson PL, Fletcher CV. Updated clinical pharmacologic considerations for HIV-1 protease inhibitors. *Curr HIV/AIDS Rep.* 2004;1(1):33-39.
6. Morse GD, Catanzaro LM, Acosta EP. Clinical pharmacodynamics of HIV-1 protease inhibitors: use of inhibitory quotients to optimise pharmacotherapy. *Lancet Infect Dis.* 2006;6(4):215-225.
7. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS.* 2003;17(8):1157-1165.
8. Fletcher CV, Acosta EP, Henry K, et al. Concentration-controlled zidovudine therapy. *Clin Pharmacol Ther.* 1998;64(3):331-338.
9. Back D, Gatti G, Fletcher C, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS.* 2002;16 Suppl 1:S5-37.
10. Acosta EP, King JR. Methods for integration of pharmacokinetic and phenotypic information in the treatment of infection with human immunodeficiency virus. *Clin Infect Dis.* 2003;36(3):373-377.
11. Ellner PD, Neu HC. The inhibitory quotient. A method for interpreting minimum inhibitory concentration data. *JAMA.* 1981;246(14):1575-1578.
12. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 2003;47(1):350-359.
13. Best B, Witt M, Goicoechea M, et al. Improved antiretroviral exposure with therapeutic drug monitoring. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 589.

14. Bossi P, Peytavin G, Ait-Mohand H, et al. GENOPHAR: a randomized study of plasma drug measurements in association with genotypic resistance testing and expert advice to optimize therapy in patients failing antiretroviral therapy. *HIV Med.* 2004;5(5):352-359.
15. Clevenbergh P, Garraffo R, Durant J, et al. PharmAdapt: a randomized prospective study to evaluate the benefit of therapeutic monitoring of protease inhibitors: 12 week results. *AIDS.* 2002;16(17):2311-2315.
16. de Requena DG, Nunez M, Gallego O, et al. Does an increase in nevirapine plasma levels cause complete virologic suppression in patients experiencing early virologic failure? *HIV Clin Trials.* 2002;3(6):463-467.
17. Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection. *AIDS.* 2002;16(4):551-560.
18. Haas DW. Can responses to antiretroviral therapy be improved by therapeutic drug monitoring? *Clin Infect Dis.* 2006;42(8):1197-1199.
19. Nettles RE, Kieffer TL, Parsons T, et al. Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring. *Clin Infect Dis.* 2006;42(8):1189-1196.

DISCONTINUATION OR INTERRUPTION OF THERAPY

General

Discontinuation of antiretroviral therapy may be indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or parent request. Although these events are usually unplanned, purposeful discontinuation of therapy has been widely used in the adult population to reduce toxicity, costs, and drug-related failure associated with antiretroviral therapy. At this time, there are minimal data in infants, children, and adolescents about planned structured treatment interruptions (STI). Thus, STI should not be attempted in children or adults outside of a clinical trial setting. The discussion below provides general guidance for the interruption of antiretroviral therapy and the risks and benefits in specific situations.

Short-Term Therapy Interruption

In the pediatric patient, short-term therapy interruptions are most often necessitated by acute illnesses that limit oral intake. These illnesses are often infectious diseases that result in vomiting and/or diarrhea. The clinician has no choice but to stop all therapy at the same time. Planned short-term interruption of therapy may also be required in the event of surgery or sedation for procedures, but when possible, the patient should be allowed to continue regular antiretroviral therapy with minimal fluid intake. If the period of restricted oral intake will be prolonged, then all therapy should be stopped at the same time if the medications have similar half-lives. In the case of serious or life-threatening antiretroviral therapy toxicity, all drugs should be stopped immediately.

When a short-term therapy interruption is indicated, all antiretroviral therapy should be stopped at the same time in most cases. This can be problematic with agents with a long half-life. Stopping agents with different half-lives at the same time can result in functional monotherapy with the drug with the longest half-life. This is particularly concerning in the case of the NNRTIs efavirenz and nevirapine.

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation *[1-4]*. As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in a slower rate of drug clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and Hispanics *[3-4]*. To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs (i.e., NRTI backbone or PI) for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known. Detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation *[4]*. An alternative is to substitute a PI for up to 4 weeks prior to the interruption of all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective

strategy. There is no information in children and, because the pharmacokinetics of these agents are different in children, the recommendations for adults may not be applicable *[5-7]*.

An additional consideration is reintroduction of nevirapine. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing CYP3A4 metabolic liver enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. Lower rates of rash toxicity have been observed with the 2-week dose escalation *[5]*. In cases where nevirapine has been discontinued for more than 2 weeks, it is recommended that another 2-week dose escalation be used when the drug is reintroduced.

Long-Term Structured Treatment Interruptions

Long-term STIs have been proposed to reduce toxicities and costs associated with long-term antiretroviral therapy. STIs have also been proposed in patients who have limited treatment options to allow a return to their wild-type virus, which may be more susceptible to treatment. At this time, there is only minimal information about STI in children. In 1 study, children with controlled viral load (HIV RNA <400 copies/mL for $\geq$12 months) were subjected to increasing intervals of treatment interruption. Of 14 children studied, 4 maintained undetectable viral loads with interruptions of up to 27 days. It has been hypothesized that enhanced HIV-specific immune responses may play a role in the viral suppression *[8]*. However, new drug-resistance mutations were detected in 3 of 14 children in the STI study.

Recently, the results of two large, randomized clinical trials in adults have demonstrated inferior responses when CD4 cell count was used as an indication to stop and start therapy. The Strategies for Management of Antiretroviral Therapy stopped antiretroviral therapy when the CD4 cell count was >350 cells/mm^3 and reintroduced therapy when the count was <250 cells/mm^3. In comparison to the group receiving continuous antiretroviral therapy, the STI group had an increased risk of disease progression and death *[9]*. Similarly, in the Trivican trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior *[10]*. However, in studies in adults using a CD4 count <350 cells/mm^3 as a trigger to restart therapy, no significant difference in serious disease progression or death was seen *[11-12]*. A large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy *[13]*. Several additional trials are currently ongoing in adults.

Many questions remain about STI in children and adolescents. In the United States and other developed countries, the majority of HIV-infected children began antiretroviral therapy during infancy *[14-15]*. Many of these children have had controlled viral replication for many years and are growing and developing normally. It is unclear if these children could discontinue therapy at some point and reinitiate based on CD4 cell decline. Although this has been speculated as plausible, there are no data to support this strategy and it should not be attempted outside of a clinical trial setting.

An additional scenario that is often raised is the patient who has limited treatment options and who, despite aggressive antiretroviral therapy, cannot reach an undetectable viral load. In these cases, interruption of therapy is generally not recommended because, despite detectable viral replication, immunologic benefit has been well documented *[16-19]*.

With either unplanned or STI therapy, the clinician should discuss the reasons and plans with the parent or guardian and, if applicable, the patient prior to proceeding. The parent and child should be made aware of the possibility of viral rebound resulting in a worsening of clinical symptoms, the risk of developing drug resistance, and the need for protection against opportunistic pathogens. The timelines and criteria for restarting therapy should be clear.

References

1. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
2. Mackie NE, Fidler S, Tamm N, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med.* 2004;5(3):180-184.
3. Nolan D, Phillips E, Mallal S. Efavirenz and CYP2B6 polymorphism: implications for drug toxicity and resistance. *Clin Infect Dis.* 2006;42(3):408-410.
4. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401-407.
5. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis.* 1996;174(4):713-721.
6. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
7. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
8. Borkowsky W, Mcfarland E, Yogev R, et al. Repeated supervised treatment interruption with progressive increases in "Off treatment" Duration results in enhanced virologic control in a subset of pediatric individuals. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 19.
9. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.
10. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in West Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet.* 2006;367(9527):1981-1989.
11. Ananworanich J, Gayet-Ageron A, Le Braz M, et al. CD4 guided scheduled treatment interruptions compared to continuous therapy: Results of the staccato trial. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 102.
12. Marchou B, Tangre P, Charreau I, et al. Structured treatment interruptions in HIV-infected patients with high CD4 cell counts and virologic suppression: Results of a prospective, randomized, open-lable trial (window-anrs 106). Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 104.
13. d'arminio Monforte A, Cozzi-Lepri A, Phillips A, et al. Interruption of highly active antiretroviral therapy in HIV clinical practice: results from the Italian Cohort of Antiretroviral-Naive Patients. *J Acquir Immune Defic Syndr.* 2005;38(4):407-416.
14. Brogly S, Williams P, Seage GR, 3rd, et al. Antiretroviral treatment in pediatric HIV infection in the United States: from clinical trials to clinical practice. *JAMA.* 2005;293(18):2213-2220.
15. Liu KL, Peters V, Weedon J, et al. Sex differences in morbidity and mortality among children with perinatally acquired human immunodeficiency virus infection in New York City. *Arch Pediatr Adolesc Med.* 2004;158(12):1187-1188.
16. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
17. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
18. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
19. Sufka SA, Ferrari G, Gryszowka VE, et al. Prolonged CD4+ cell/virus load discordance during treatment with protease inhibitor-based highly active antiretroviral therapy: immune response and viral control. *J Infect Dis.* 2003;187(7):1027-1037.

Antiretroviral Drug-Resistance Testing

(Updated August 16, 2010)

Panel's Recommendations:

- ***Antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children (AII).***
- ***Antiretroviral drug-resistance testing is recommended prior to changing therapy for treatment failure (AI*).***
- ***Resistance testing in the setting of virological failure should be obtained while the patient is still on the failing regimen or within 4 weeks of discontinuing the regimen (AII*).***
- ***The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, especially if the antiretroviral agent shares cross resistance with drugs previously used. In addition, current resistance assays are not sensitive enough to fully exclude the presence of resistant virus. Thus, previously used antiretroviral agents and previous resistance tests should be reviewed when making decisions regarding the choice of new agents for patients with virologic failure (AII).***
- ***Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered (AI*). Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (AI*).***
- ***Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral regimen in a pediatric patient (AI*).***

OVERVIEW OF HIV DRUG-RESISTANCE AND RESISTANCE ASSAYS

HIV replication is a continuous process in most untreated patients, leading to the daily production of billions of viral particles. The goal of antiretroviral therapy is to suppress HIV replication as rapidly and fully as possible, indicated by a reduction in plasma HIV RNA to below the limit of detection of the most sensitive assays available (<50–70 copies/mL). Unfortunately, mutations in HIV RNA readily arise during viral replication because HIV reverse transcriptase is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral drugs readily and progressively selects for strains of HIV with mutations that confer drug resistance.

Drug-resistance detection methods vary depending on the class of antiretroviral agents. Both genotypic assays and phenotypic assays are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase (RT), integrase, or protease (PR). Viral coreceptor (tropism) assays, a form of phenotypic assay, have been successfully employed in detecting the presence of virus with tropism that will (R5 tropism) or will not (X4 or mixed tropism) respond to CCR5 antagonists. Clinical experience with testing for viral resistance to other agents is more limited, but genetic mutations associated with resistance to integrase strand transfer inhibitors have been identified, and a commercial phenotypic assay is available for evaluation of resistance to the fusion inhibitor enfuvirtide (T20). Experience is also limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug resistance in patients infected with non-B subtypes of HIV *[1]*.

Genotypic Assays

Genotypic assays for resistance to RT, PR, and integrase strand transfer inhibitors are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and integrase coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance-associated mutations in plasma samples containing approximately 1,000 copies/mL or more of HIV RNA, and results are generally available within 1–2 weeks of sample collection *[2]*. Interpretation of test results requires knowledge of the mutations selected by different antiretroviral drugs and of the potential for cross resistance to other drugs conferred by certain

mutations. For some drugs, there is a low genetic barrier to the development of resistance, and a single nucleotide mutation is enough to confer high-level resistance sufficient to remove any clinical utility. This is exemplified by resistance to nevirapine resulting from mutations in the HIV reverse transcriptase. Other mutations lead to drug resistance but simultaneously impair HIV replication. Clinically useful activity of the antiretroviral agent may therefore remain, as demonstrated by evidence of continued clinical benefit from lamivudine in individuals with evidence of the high-level resistance engendered by the M184V reverse transcriptase mutation *[3]*. Other mutations have little direct effect on resistance but arise during HIV evolution to high-level resistance or improve the replication of virus-bearing mutations that confer high-level resistance to an antiretroviral agent.

The International AIDS Society-USA (IAS-USA), the Los Alamos HIV Drug Resistance Database, and the Stanford University HIV Drug Resistance Database maintain lists of significant resistance-associated mutations relevant to currently available antiretroviral drugs (see **http://www.iasusa.org/resistance_mutations**, **http://hiv-web.lanl.gov** or **http://hivdb.stanford.edu**). A variety of online tools that take into account the ability of some mutations selected by one drug to cause partial or full cross resistance with other drugs are now available to assist the provider in interpreting genotypic test results. Although the response to antiretroviral therapy in children and adolescents is not always predicted by the results of genotypic resistance assays, clinical trials in adults have demonstrated the benefit of resistance testing combined with consultation with specialists in HIV drug resistance in improving virologic outcomes *[2, 4-10]*. Given the potential complexity of interpretation of genotypic resistance, it is recommended that clinicians consult with a specialist in pediatric HIV infection for assistance in the interpretation of genotypic results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic resistance assays provide a more direct assessment of the impact of mutations acquired by mixture of virus strains present in an individual. As they are most often performed, phenotypic assays involve PCR amplification of the reverse transcriptase, integrase, protease, or other HIV gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a laboratory strain of HIV. Replication of this recombinant virus at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration, or IC50) is calculated, and the ratio of the IC50 of test and reference viruses is reported as the fold increase in IC50 (i.e., fold resistance change). Automated, recombinant phenotypic assays are commercially available with results available in 2–3 weeks but are more costly than genotypic assays. In addition, interpretation of phenotypic assay results is sometimes complicated by the paucity of information about outcomes with specific levels of resistance.

Analytic techniques have also been developed to use the genotype to predict the likelihood of a drug-resistant phenotype. This bioinformatic approach, currently applicable for reverse transcriptase and protease inhibitor resistance only, matches the pattern of mutations obtained from the patient sample with a large database of samples for which both genotype and phenotype are known. Thus, the sample is assigned a predicted phenotype susceptibility (or "virtual phenotype") based on the data from specimens matching the patient's genotype. The primary limitation of this approach is that predictive power depends upon the number of matched phenotypic and genotypic assays, which may be limited for newer drugs.

Tropism (Viral Coreceptor Use) Assays

HIV enters cells by a complex multistep process that involves sequential interactions between the HIV envelope protein molecules and the CD4 receptor, then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses in the majority of untreated individuals, including infants and children infected by mother-to-child transmission of HIV, are initially CCR5 tropic. However, a shift in coreceptor tropism often occurs over time, from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (dual- or mixed-tropic; D/M-tropic). Antiretroviral-treated patients with extensive drug resistance are more likely to harbor detectable X4- or D/M-tropic virus than untreated patients with comparable CD4 T-cell counts *[11]*.

Resistance to CCR5 antagonists is currently detected using the specialized phenotypic assay methods Phenoscript (VIRalliance, Paris, France) and Trofile (Monogram Biosciences, Inc). These assays involve the generation of recombinant viruses bearing patient-derived envelope proteins (gp120 and gp41). The relative capacity of these pseudoviruses to infect cells bearing the cell surface proteins CCR5 or CXCR4 is quantified based on the expression of a reporter gene. The Trofile assay takes about 2 weeks to perform and requires a plasma viral load ≥1,000 copies/mL. The initial version of the Trofile assay used during the clinical trials that led to the licensure of maraviroc was able to detect X4-tropic virus with 100% sensitivity when present at a frequency of 10% of the plasma virus population but only 83% sensitivity when the variant was present at a frequency of 5%. In initial clinical trials of CCR5 antagonist drugs, this sensitivity threshold was not always sufficient to exclude the presence of clinically meaningful levels of X4- or D/M-tropic virus in patients initiating a CCR5 inhibitor-based regimen. A newer version of the Trofile assay with improved sensitivity able to detect X4- or D/M-tropic virus representing as little as 0.3% of the plasma virus is now available *[12-13]*. Genotypic assays that may also prove useful in detection of X4 or D/M tropism are also under development. The detection of any usage of CXCR4 is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor use assays should be performed prior to the use of a CCR5 inhibitor and may be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc.

Use of Resistance Assays in Determining Initial Treatment

Mother-to-child transmission and horizontal transmission of drug-resistant HIV strains have been well documented and are associated with suboptimal virologic response to initial antiretroviral therapy *[14-18]*. Drug-resistant variants of HIV may persist for months after birth in infected infants *[19]* and impair the response to antiretroviral therapy *[20]*. Consequently, antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.

Use of Resistance Assays in the Event of Virologic Failure

Several studies *[2, 4-10]* have been performed in adults indicating that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Although not yet confirmed in children *[21]*, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure. Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction because virologic failure in the setting of combination antiretroviral therapy may be associated with resistance to only one component of the regimen *[1]*. Poor adherence should be suspected when no evidence of resistance to a failing regimen is identified.

Limitations of Current Resistance and Tropism Assays

Limitations of the genotypic, phenotypic, and phenotype-prediction assay approaches include lack of uniform quality assurance testing and high cost. In addition, drug-resistant viruses that constitute <10%–20% of the circulating virus population may not be detected by any of the currently available assays. Consequently, a review of the past use of antiretroviral agents is important in making decisions regarding the choice of new agents for patients with virologic failure.

Although drug resistance may be detected in infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4–6 weeks after antiretroviral drugs are stopped *[22-24]*. As a result, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued. The absence of detectable resistance to a drug at the time of testing does not ensure that future use of the drug will be successful *[25]*, especially if the agent shares cross resistance with drugs previously used. It may be prudent to repeat resistance testing if an incomplete virological response to a new treatment regimen is observed in an individual with prior treatment failure(s) (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

References

1. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis.* 2008;47(2):266-285.
2. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet.* 1999;353(9171):2195-2199.
3. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis.* 2005;41(2):236-242.
4. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 2000;14(9):F83-93.
5. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS.* 2002;16(3):369-379.
6. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS.* 2002;16(4):579-588.
7. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS.* 2002;16(5):727-736.
8. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of care (Narval trial, ANRS 088). *Antivir Ther.* 2003;8(5):427-434.
9. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis.* 2004;38(5):723-730.
10. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.* 2002;16(2):209-218.
11. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis.* 2006;194(7):926-930.
12. Su Z, Gulick RM, Krambrink A, et al. Response to vicriviroc in treatment-experienced subjects, as determined by an enhanced-sensitivity coreceptor tropism assay: reanalysis of AIDS clinical trials group A5211. *J Infect Dis.* 2009;200(11):1724-1728.
13. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis.* 2010;201(6):803-813.
14. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses.* 2007;23(8):988-995.
15. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
16. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis.* 2008;197(6):867-870.
17. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr.* 2006;43(5):535-540.
19. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
20. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
21. Green H, Gibb DM, Compagnucci A, et al. A randomized controlled trial of genotypic HIV drug resistance testing in HIV-1-infected children: the PERA (PENTA 8) trial. *Antivir Ther.* 2006;11(7):857-867.
22. Devereux HL, Youle M, Johnson MA, et al. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS.* 1999;13(18):F123-127.

23. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS.* 2000;14(18):2857-2867.
24. Verhofstede C, Wanzeele FV, Van Der Gucht B, et al. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS.* 1999;13(18):2541-2546.
25. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis.* 2006;194(9):1309-1318.

Conclusion

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral drugs and newer classes of drugs are approved. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional antiretroviral drugs become approved and optimal use of these drugs in children becomes better understood, the Panel will modify these guidelines. It should be noted that guidelines are only a starting point for medical decision making and are not meant to supersede the judgment of clinicians experienced in the care of HIV-infected children. Because of the complexity of caring for HIV-infected children, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist.

The Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of the Infectious Disease Society of America, the Pediatric Infectious Disease Society, and the American Academy of Pediatrics jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children; these guidelines are available at **http://aidsinfo.nih.gov** *[1]*. Similar guidelines for adults are also available at the same Web site *[2]*.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
2. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.

Appendix A: Financial Disclosure for Members of HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children – January 2010

Name	Panel Status	Company	Relationship
Elaine S. Abrams	M	NONE	N/A
Edmund Capparelli	M	Cadence Pharmaceuticals Bristol-Myers Squibb Pharmaceuticals GlaxoSmithKline Pharmaceuticals Arpida Pharmaceuticals Johnson & Johnson	• Consultant • Consultant • Travel Support • Consultant • Consultant
Diana Clarke	M	NONE	N/A
Kenneth L. Dominguez	HHS	NONE	N/A
Brian Feit	HHS	NONE	N/A
Patricia M. Flynn	M	Tibotec	• Clinical TrialsAgreement
Marc D. Foca	M	Cellestis	• Honoraria (Participated in an expert panel discussion and received a single honorarium.)
Edward Handelsman	HHS	NONE	N/A
Peter Havens	C	Roche Gilead Biotech Pharmaceuticals National Institute of Child Health and Human Development (NICHD) HHS	• Consultant • Other: Research Collaboration • Other: Research Collaboration • Research Support: Adolescent Trials Network • Advisory Board • Other: Pediatric Guidelines
Rohan Hazra	HHS	NONE	N/A
Nancy Hutton	M	NONE	N/A
Patrick Jean-Philippe	HHS	NONE	N/A

Name	Panel Status	Company	Relationship
Ebony Johnson	M	NONE	N/A
Paul A. Krogstad	M	NONE	N/A
Linda Lewis	HHS	NONE	N/A
James McAuley	M	NONE	N/A
Mark Mirochnick	M	NONE	N/A
Lynne Mofenson	ES	NONE	N/A
Paul Palumbo	M	NONE	N/A
Mary E. Paul	M	NONE	N/A
Vicki Peters	M	NONE	N/A
Richard M. Rutstein	M	Bristol-Myers Squib Pharmaceuticals Tibotec	• Advisory Board • Research Support
Dorothy Shaw	M	NONE	N/A
George Siberry	HHS	NONE	N/A
Russell Van Dyke	C	NONE	N/A
Geoffrey A. Weinberg	C	MedImmune, Inc. Merck Vaccines Sanofi Pasteur Vaccines GlaxoSmithKline Vaccines	• Advisory Board • Speakers' Bureau • Speakers' Bureau • Speakers' Bureau
Andrew Wiznia	M	Gilead Sciences Argos Therapeutics	• Consultant • Advisory Board

Key to Abbreviations: C = Co-Chair; ES = Executive Secretary; M = Member; HHS = Member from HHS; N/A = Not applicable

Appendix B: Pediatric Antiretroviral Drug Information

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir (ABC, Ziagen)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 20 mg/mL
Tablets: 300 mg (scored)
Combination tablets:
- *with lamivudine (3TC)*: 600 mg ABC + 300 mg 3TC (Epzicom)
- *with zidovudine (ZDV) and lamivudine (3TC)*: 300 mg ABC + 300 mg ZDV + 150 mg 3TC (Trizivir)

Dosing Recommendations

Neonate/Infant dose:
Not approved for infants <3 months of age.

Pediatric dose:
Oral solution (≥3 months):
8 mg/kg (maximum 300 mg) twice daily

Scored 150 mg tablet (≥14 kg):

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	PM Dose	Total Daily Dose
14–21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21–<30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (≥16 years)/Adult dose:
300 mg twice daily or 600 mg once daily

Dosing Recommendations for Combination Formulations

Trizivir
Adolescent (≥40 kg)/Adult dose:
One tablet twice daily

Epzicom
Adolescent (>16 years)/Adult:
One tablet once daily

Selected Adverse Events

- Hypersensitivity reaction that may be fatal; symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath.
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

- Can be given without regard to food.
- Caution patients and parents about the risk of serious hypersensitivity reaction that can be fatal. Do not rechallenge.
- Test patients for the HLA-B*5701 allele prior to starting therapy to predict risk of hypersensitivity; patients with the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B+5701 testing who are tolerating ABC do not need to be tested.

Metabolism

- Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%.
- ABC requires dosage adjustment in hepatic insufficiency. Do not use Trizivir and Epzicom (fixed-dose combination products) in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):
- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should not cause changes in clearance of agents metabolized through these pathways, such as PIs and NNRTIs.
- Abacavir is metabolized by alcohol dehydrogenase and glucuronyltransferase. Alcohol increases abacavir levels by 41%.

Major Toxicities:
- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by rash or by signs or symptoms in two or more of the following groups: (1) fever; (2)

constitutional, including malaise, fatigue, or achiness; (3) gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain; or (4) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. If a hypersensitivity reaction is suspected, abacavir should be stopped and **not restarted because hypotension and death have occurred upon rechallenge**. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.

- *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ABC.html**).

Pediatric Experience: Abacavir has been studied in HIV-infected children both separately and in combination with other antiretroviral drugs *[1-11]*. In the PENTA-5 trial, 130 HIV-infected antiretroviral-naïve children were randomly assigned to 1 of 3 different nucleoside analogue regimens: zidovudine/lamivudine, abacavir/zidovudine, and abacavir/lamivudine, with and without nelfinavir *[10]*. The 2 abacavir-containing regimens were associated with greater mean viral load decreases after 48 weeks of therapy than the zidovudine/lamivudine regimen (-1.71, -2.17, and -2.63 log copies/mL with zidovudine/lamivudine, abacavir/zidovudine, and abacavir/lamivudine, respectively). In this study, 4 children (3%) stopped abacavir due to a possible hypersensitivity reaction. After 5 years of follow-up in the PENTA-5 study, children who were treated with abacavir/lamivudine were significantly more likely to have HIV RNA levels <50 copies/mL than children treated with zidovudine/lamivudine or abacavir/ zidovudine (63% vs. 25 % or 32%, p = 0.003) and had significantly better improvement in height for age and weight for age *[5]*.

Pharmacokinetic studies of abacavir in children <12 years of age have demonstrated that children have more rapid clearance than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure *[4, 6]*. Adolescents and young adults (ages 13 to 25) have clearance that is slower than younger children but still more rapid than that found in adults *[12]*. The PENTA-13 trial studied once-daily versus twice-daily dosing of abacavir in combination with lamivudine in 24 children age 2–13 years, with undetectable or low, stable virus load at the time of starting once-daily therapy, showing equivalent $AUC_{0\text{-}24}$ for both drugs and improved acceptability in the once-daily dosing arm *[1, 8]*. However, trough concentrations were lower for both abacavir and lamivudine in younger children (ages 2–6 years) receiving the once-daily regimen *[1]*. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of abacavir and lamivudine can be effectively used in children.

In pediatric populations, triple-NRTI-only combinations should be used only in special circumstances. In 1 study of 205 treatment-experienced children ranging in age from 0.7 to 13 years, only 10% of 102 children receiving abacavir/ zidovudine/lamivudine had HIV RNA concentrations <400 copies/mL after 48 weeks of therapy *[11]*. Several studies of abacavir as part of a PI-sparing 3-drug NRTI regimen (zidovudine, lamivudine, and abacavir) have been done in adults and show decreased antiretroviral potency of the triple-NRTI-only regimens *[13-17]*.

References

1. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr.* 2005;39(1):63-68.
2. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther.* 2005;10(2):239-246.
3. Capparelli EV, Letendre SL, Ellis RJ, et al. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother.* 2005;49(6):2504-2506.
4. Cross SJ, Rodman JH, Lindsey JC, et al. Abacavir and metabolite pharmacokinetics in HIV-1-infected children and adolescents. *J Acquir Immune Defic Syndr.* 2009;51(1):54-59.
5. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
6. Hughes W, McDowell JA, Shenep J, et al. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrobial Agents Chemother.* 1999;43(3):609-615.

7. Kline MW, Blanchard S, Fletcher CV, et al. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. AIDS Clinical Trials Group 330 Team. *Pediatrics.* 1999;103(4):e47.
8. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J.* 2006;25(6):533-537.
9. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
10. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
11. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
12. Sleasman JW, Robbins BL, Cross SJ, et al. Abacavir pharmacokinetics during chronic therapy in HIV-1-infected adolescents and young adults. *Clin Pharmacol Ther.* 2009;85(4):394-401.
13. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
14. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
15. Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naive HIV-infected patients. *AIDS Patient Care STDS.* 2005;19(3):135-140.
16. Kumar PN, Salvato P, Lamarca A, et al. A randomized, controlled trial of initial anti-retroviral therapy with abacavir/lamivudine/zidovudine twice-daily compared to atazanavir once-daily with lamivudine/zidovudine twice-daily in HIV-infected patients over 48 weeks (ESS100327, the ACTION Study). *AIDS Res Ther.* 2009;6:3.
17. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350(18):1850-1861.

Didanosine (ddI, Videx)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Videx pediatric powder for oral solution: reconstituted 10 mg/ml
Videx EC delayed-release capsules (enteric-coated beadlets): 125 mg, 200 mg, 250 mg, and 400 mg
Generic ddI delayed-release capsules: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/Infant dose (2 weeks to <3 months):
50 mg/m^2 of body surface area every 12 hours
(Manufacturer recommends 100 mg/m^2 of body surface area every 12 hours in this age range. Panel members interpret PK data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 of body surface area every 12 hours.)

Infant dose (>3 months to 8 months):
100 mg/m^2 of body surface area every 12 hours

Pediatric usual dose of oral solution (>8 months):
120 mg/m^2 of body surface area every 12 hours
(Dose range: 90–150 mg/m^2 of body surface area every 12 hours)

Pediatric dose of Videx EC or generic capsules (6–18 years and ≥20 kg):

Body Weight (kg)	Dose
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

In treatment-naïve children 3–21 years of age, 240 mg/m^2 of body surface area once daily (oral solution or capsules) has been used with good viral suppression.

Adolescent/Adult dose:
<60 kg: 250 mg once daily
≥60 kg: 400 mg once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

ddI in combination with tenofovir (TDF)

Pediatric/Adolescent dose:
No data on combination in children or adolescents <18 years of age.

Adult dose:
<60 kg (limited data in adults): 200 mg once daily
≥60 kg: 250 mg once daily

Selected Adverse Events

- Peripheral neuropathy (dose related)
- Electrolyte abnormalities and hyperuricemia
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported (increased risk when used in combination with stavudine [d4T])
- Pancreatitis (dose related, less common in children than adults, more common in adults when used in combination with TDF or d4T)
- Potential association with noncirrhotic portal hypertension

Special Instructions

- Food decreases absorption of all ddI preparations; administer ddI on an empty stomach (30 minutes before or 2 hours after a meal).
- ddI oral solution contains antacids that may interfere with the absorption of other medications.
- Shake oral solution well. Keep refrigerated; admixture is stable for 30 days.
- When coadministered, ddI delayed-release capsule formulation and TDF may be taken under fasted conditions or with a light meal.

Metabolism

- Renal excretion 50%.
- Dosing of ddI in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)*:*

- *Absorption:* The presence of antacids in the didanosine suspension has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by the appropriate timing of doses.
- *Mechanism unknown:* Didanosine serum concentrations are increased when coadministered with tenofovir.
- *Renal elimination:* Drugs that decrease renal function could decrease clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* There is increased risk of pancreatitis and peripheral neuropathy with some NRTIs (e.g., stavudine). Combination of stavudine and didanosine is not recommended (unless the benefits clearly outweigh the risks) because of overlapping toxicities and reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis (dose related, less common in children than adults, more common in adults when used in combination with tenofovir), increased liver enzymes, and retinal depigmentation have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefit clearly outweighs the potential risk.
- *Rare:* Noncirrhotic portal hypertension, with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use in adults [1].

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ddI.html**).

Pediatric Experience: Didanosine has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[2-24]*. Recommended didanosine doses in children have traditionally been 90–150 mg per meter^2 body surface area per dose twice daily. Doses higher than 180 mg per meter^2 body surface area twice daily are associated with increased toxicity *[3]*. In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg per meter^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with a predicted 88% of patients at a dose of 120 mg per meter^2 body surface area *[6]*. This dose of 120 mg per meter^2 body surface area per dose twice daily has therefore become the "standard" dose of didanosine for older infants and children. Data from multiple pediatric studies of didanosine alone or in combination with other drugs, including a study of long-term didanosine use (median duration of almost 2 years), show that didanosine appears safe and is associated with clinical improvement, increase in CD4 count, and decrease in viral load *[5, 7-8, 11, 13, 15, 19]*.

Three major areas of controversy remain in the use of didanosine in the treatment of children with HIV infection: (1) the appropriate dose to use in infants 2 weeks to 4 months of age, (2) the need to dose didanosine on an empty stomach, and (3) the potential use of enteric-coated didanosine (Videx EC) once daily in children.

The "usual pediatric dose" of 120 mg per meter^2 body surface area per dose twice daily was used successfully in combination therapy in infants 2 to 16 months of age without significant toxicity *[18]*. Currently, the FDA recommends 100 mg per meter^2 body surface area per dose twice daily for infants from 2 weeks to 8 months of age, increasing to 120 mg per meter^2 body surface area per dose twice daily at age 8 months. However, two small studies suggest that higher AUCs are seen in infants <6 weeks of age and that a dose of 100 mg per meter^2 body surface area per day (either as 50 mg per meter^2 body surface area per dose twice daily or 100 mg per meter^2 body surface area once daily) achieves AUCs consistent with those of higher doses in older children *[9, 12]*. Therefore, because of pharmacokinetic differences in younger infants (2 weeks to 4 months) compared with older children, a dose of 50 mg per meter^2 of body surface area twice daily may be more appropriate in younger infants.

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and may decrease medication compliance by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption *[20]*. To improve compliance, some practitioners recommend administration without regard to timing of

meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Enteric-coated didanosine (Videx EC) administered as a single dose of 240 mg per meter^2 body surface area once daily has been shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine *[9]*. The resultant intracellular (active) drug concentrations are unknown. In 24 children with HIV infection, didanosine at a dose of 180 mg per meter^2 body surface area once daily was compared with 90 mg per meter^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group *[2]*. In fact, in 53 children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg per meter^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was poorer in the children given once-daily therapy *[14]*. A European trial of once-daily combination therapy in 36 children 3–11 years of age that included didanosine at a dose of 200–240 mg per meter^2 demonstrated safety and efficacy with 96 weeks of follow-up data *[25]*. Enteric-coated didanosine is currently approved for use in children ages 6 to 18 years who are able to swallow capsules whole and have a body weight of at least 20 kg.

In a study in the United States, long-term virologic suppression with a once daily regimen of efavirenz, emtricitabine, and didanosine (enteric-coated beadlet capsules) was reported in 37 treatment-naïve children, 3–21 years of age, participating in PACTG 1021 *[26]*. The didanosine dose used in that study was 240 mg/ meter^2/dose once daily, and pharmacokinetic analysis showed no dose changes were needed to reach PK targets *[26]*. Eighty-five percent of subjects were able to achieve HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy.

References

1. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis.* 2009;49(4):626-635.
2. Abreu T, Plaisance K, Rexroad V, et al. Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2000;44(5):1375-1376.
3. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med.* 1991;324(3):137-144.
4. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
5. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med.* 1997;336(24):1704-1712.
6. Fletcher CV, Brundage RC, Remmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother.* 2000;44(4):1029-1034.
7. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS.* 1999;13(13):1653-1658.
8. Gibb D, Barry M, Ormesher S, et al. Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection. *Br J Clin Pharmacol.* 1995;39(5):527-530.
9. King JR, Nachman S, Yogev R, et al. Single-dose pharmacokinetics of enteric-coated didanosine in HIV-infected children. *Antivir Ther.* 2002;7(4):267-270.
10. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
11. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.
12. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J.* 2005;24(6):503-509.
13. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
14. Marchisio P, Principi N, Gabiano C, et al. Once versus twice daily administration of didanosine in children with symptomatic HIV-associated disease who were intolerant to or clinically deteriorated on zidovudine. The Italian Pediatric Collaborative Study Group on Didanosine. *Antivir Ther.* 1997;2(1):47-55.

15. McKinney RE Jr, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
16. Mueller BU, Butler KM, Stocker VL, et al. Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics.* 1994;94(5):724-731.
17. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
18. Rongkavilit C, Thaithumyanon P, Chuenyam T, et al. Pharmacokinetics of stavudine and didanosine coadministered with nelfinavir in human immunodeficiency virus-exposed neonates. *Antimicrob Agents Chemother.* 2001;45(12):3585-3590.
19. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.
20. Stevens RC, Rodman JH, Yong FH, et al. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(5):415-421.
21. Hirt D, Bardin C, Diagbouga S, et al. Didanosine population pharmacokinetics in West African human immunodeficiency virus-infected children administered once-daily tablets in relation to efficacy after one year of treatment. *Antimicrob Agents Chemother.* 2009;53(10):4399-4406.
22. Balis FM, Pizzo PA, Butler KM, et al. Clinical pharmacology of 2',3'-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis.* 1992;165(1):99-104.
23. Butler KM, Venzon D, Henry N, et al. Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics.* 1993;91(4):747-751.
24. Whitcup SM, Butler KM, Caruso R, et al. Retinal toxicity in human immunodeficiency virus-infected children treated with 2',3'-dideoxyinosine. *Am J Ophthalmol.* 1992;113(1):1-7.
25. Scherpbier HJ, Bekker V, Pajkrt D, et al. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics.* 2007;119(3):e705-715.
26. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.

Emtricitabine (FTC, Emtriva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 10 mg/mL
Capsules: 200 mg
Combination tablets
- *With tenofovir (TDF):* 200 mg FTC + 300 mg TDF (*Truvada*)
- *With TDF and efavirenz (EFV):* 200 mg FTC + 300 mg TDF + 600 mg EFV (*Atripla*)

Dosing Recommendations

Neonate/Infant Dose (0–3 months):
Oral solution: 3 mg/kg once daily

Pediatric Dose (3 months–17 years):
Oral solution: 6 mg/kg (maximum dose 240 mg) once daily
Capsules (>33 kg): 200 mg once daily

Adolescent (≥18 years)/Adult dose:
Oral solution: 240 mg (24 mL) once daily
Capsules: 200 mg once daily

Dosing Recommendations for Combination Formulations

Truvada
Adult dose:
1 tablet once daily

Atripla
Adult dose:
1 tablet once daily

Selected Adverse Events

- Nausea, diarrhea
- Hyperpigmentation/skin discoloration on palms and/or soles, predominantly observed in nonwhite patients

Special Instructions

- Can be given without regard to food. Because Atripla contains EFV, administer the drug on an empty stomach.
- Oral solution can be kept at room temperatures up to 77°F (25°C) if used within 3 months; refrigerate for longer term storage.
- Screen patients for hepatitis B virus prior to use of FTC. Severe acute exacerbation of hepatitis can occur when FTC is discontinued; monitor hepatic function for several months after therapy with FTC is stopped.

Metabolism

- Limited metabolism: No CYP450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***
- *Other NRTIs:* Do not use in combination with lamivudine because of the similar resistance profiles and no additive benefit.
- *Renal elimination:* Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance.

Major Toxicities:
- *More common:* Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children).
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in HIV/HBV-coinfected patients changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/FTC.html**).

Pediatric Experience: A single-dose pharmacokinetic study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children 2–17 years of age *[1]*. Emtricitabine was found to be well absorbed following oral administration, with a

mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg emtricitabine once-daily dose were approximately equivalent to those in adults receiving the standard 200-mg dose.

Based on this dose-finding study, emtricitabine was given at a dose of 6 mg/kg once daily in combination with other antiretroviral drugs *[2-3]*. In a pediatric Phase II study, 71 antiretroviral-naïve children received emtricitabine plus stavudine and lopinavir/ritonavir while 45 treatment-experienced children were maintained on their initial regimens, but changed from lamivudine to emtricitabine *[3]*. Pharmacokinetic results were similar to the preceding dose-finding study *[1]*. Follow-up data extending to Week 96 indicated that 89% of the antiretroviral-naïve and 76% of the antiretroviral-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (74% and 62%, respectively, at <50 copies/mL). Grade 3 or 4 laboratory abnormalities were found in 2.9% of the study population, and serious adverse events possibly related to emtricitabine were found to be 1.2% after 164 weeks of follow-up.

Emtricitabine was studied in PACTG P1021 at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with didanosine and efavirenz, all given once daily, in 37 antiretroviral-naïve HIV-infected children age 3 months to 21 years *[2]*. This regimen was well tolerated, and emtricitabine and didanosine concentrations met the desired target study concentrations. Eighty-five percent of subjects achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 count rose by 329 cells/mm^3 at week 96.

A study in South Africa evaluated the pharmacokinetics of emtricitabine in 20 HIV-exposed infants age <3 months, given as 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks *[4]*. Emtricitabine exposure (AUC) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients age >3 months receiving the recommended dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200 mg emtricitabine dose (AUC approximately 10 hr*ug/mL). Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug. No safety issues were identified in this short pharmacokinetics study; however, extensive safety data are lacking in this age group.

References

1. Wang LH, Wiznia AA, Rathore MH, et al. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):183-191.
2. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
3. Saez-Llorens X, Violari A, Ndiweni D, et al. Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. *Pediatrics.* 2008;121(4):e827-835.
4. Blum M, Ndiweni D, Chittick G, et al. Steady state pharmacokinetic evaluation of emtricitabine in neonates exposed to HIV in utero. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI); February 5-9, 2006; Denver, CO. Abstract 568.

Lamivudine (3TC/Epivir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral Solution: 10 mg/mL (Epivir); 5 mg/mL (Epivir HBV[1])
Tablets: 150 mg (scored) and 300 mg (Epivir); 100 mg (Epivir HBV[1])
Combination Tablets:

- *With zidovudine (ZDV):* 150 mg 3TC + 300 mg ZDV (Combivir)
- *With abacavir (ABC):* 300 mg 3TC + 600 mg ABC (Epzicom)
- *With ZDV and ABC:* 150 mg 3TC + 300 mg ZDV + 300 mg ABC (Trizivir)

[1] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The formulation and dosing of 3TC in Epivir HBV are not appropriate for patients coinfected with HIV and HBV. If Epivir HBV used in HIV-infected patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen. The Epivir HBV tablet could be used in a child who requires a 100-mg 3TC dose for treatment of HIV infection.

Dosing Recommendations

Epivir (Oral Solution and Tablets)

Neonate/infant dose (<4 weeks) for prevention of transmission or treatment: 2 mg/kg twice daily

Pediatric dose (>4 weeks): 4 mg/kg (up to 150 mg) twice daily

Pediatric dosing for scored 150-mg tablet (weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21–<30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (≥16 years)/Adult dose:
Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily
Body weight <50 kg: 4 mg/kg (up to 150 mg) twice daily

Dosing Recommendations for Combination Formulations

Combivir
Adolescent (weight ≥30 kg)/Adult dose:
1 tablet twice daily

Trizivir
Adolescent (weight >40 kg)/Adult dose:
1 tablet twice daily

Epzicom
Adolescent (age >16 years)/Adult dose:
1 tablet once daily

Selected Adverse Events

- Minimal toxicity

Special Instructions

- Can be given without regard to food.
- Store oral solution at room temperature.
- Screen patients for HBV infection before starting therapy; exacerbation of hepatitis has been reported after discontinuation of 3TC. HIV/HBV-coinfected patients should have close clinical and laboratory monitoring for at least several months after stopping therapy with 3TC.

Metabolism

- Renal excretion – dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (see also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- *Renal elimination*: Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other NRTIs:* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit *[1]*.

Major Toxicities:

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, pancreatitis, lipodystrophy/lipoatrophy.
- *Rare:* Increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/3TC.html**).

Pediatric Experience: Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response *[2-17]*. Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone, most often with zidovudine, as part of a combination antiretroviral drug regimen *[3-4, 6-7, 11-12, 14, 16-17]*. In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy *[18]*. Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life *[11]*. Recently, weight band dosing recommendations for lamivudine have been developed *[19-20]*.

Few data are available regarding once-daily administration of lamivudine in children. The pharmacokinetics of once-daily versus twice-daily dosing of lamivudine (8 mg/kg once daily vs. 4 mg/kg twice daily) and abacavir (16 mg/kg once daily vs. 8 mg/kg twice daily) were evaluated in 20 HIV-infected children age 2–13 years in the PENTA-13 trial (all were stable on twice-daily therapy prior to randomization). The plasma AUC_{0-24} for both drugs was similar with once- and twice-daily administration, but trough concentrations were lower for both abacavir and lamivudine in younger children (age 2–6 years) receiving the once-daily regimen, as were peak (C_{max}) concentrations for lamivudine *[2]*. No major toxicities were noted, and there was improved acceptability of the once-daily dosing regimen *[2]*. Lamivudine undergoes intracellular metabolism to its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unmetabolized lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once-daily and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents ≥16 years and ≥50 kg *[21-22]*. More studies are needed to confirm that once-daily dosing of abacavir and lamivudine can be safely used in children.

References

1. Anderson PL, Lamba J, Aquilante CL, et al. Pharmacogenetic characteristics of indinavir, zidovudine, and lamivudine therapy in HIV-infected adults: a pilot study. *J Acquir Immune Defic Syndr.* 2006;42(4):441-449.
2. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther.* 2005;10(2):239-246.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
5. Horneff G, Adams O, Wahn V. Pilot study of zidovudine-lamivudine combination therapy in vertically HIV-infected antiretroviral-naive children. *AIDS.* 1998;12(5):489-494.
6. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
7. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.

8. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J.* 2006;25(6):533-537.
9. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch-Human Immunodeficiency Virus Working Group. *J Infect Dis.* 1996;174(1):16-25.
10. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
11. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
12. Mueller BU, Lewis LL, Yuen GJ, et al. Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 1998;42(12):3187-3192.
13. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
14. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
15. PENTA. A randomized double-blind trial of the addition of lamivudine or matching placebo to current nucleoside analogue reverse transcriptase inhibitor therapy in HIV-infected children: the PENTA-4 trial. Paediatric European Network for Treatment of AIDS. *AIDS.* 1998;12(14):F151-160.
16. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
17. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
18. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
19. World Health Organization (WHO). Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: Report of the WHO paediatric antiretroviral working group. 2008; http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.
20. L'Homme R F, Kabamba D, Ewings FM, et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS.* 2008;22(5):557-565.
21. Yuen GJ, Lou Y, Bumgarner NF, et al. Equivalent steady-state pharmacokinetics of lamivudine in plasma and lamivudine triphosphate within cells following administration of lamivudine at 300 milligrams once daily and 150 milligrams twice daily. *Antimicrob Agents Chemother.* 2004;48(1):176-182.
22. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522.

Stavudine (d4T, Zerit)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral solution: 1 mg/mL
Capsules: 15 mg, 20 mg, 30 mg, and 40 mg
Generic: Stavudine capsules and solution have been approved by the FDA for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/Infant dose (birth to 13 days):
0.5 mg/kg twice daily

Pediatric dose (14 days and up to 30 kg):
1 mg/kg twice daily

Adolescent (≥30 kg)/Adult dose:
30 to <60 kg: 30 mg twice daily
≥60 kg: 40 mg twice daily

Selected Adverse Events

- Peripheral neuropathy
- Fat maldistribution
- Pancreatitis
- Lactic acidosis with hepatic steatosis (higher incidence than with other NRTIs)
- Hyperlipidemia
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- Can be given without regard to food.
- Shake oral solution well. Keep refrigerated; will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other NRTIs*: Stavudine should not be administered in combination with zidovudine due to virologic antagonism.
- *Overlapping toxicities*: Combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Reported toxicities are more often reported in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis), particularly in adults including pregnant women. This combination should not be used for initial therapy.
- *Rare:* Increased liver enzymes, rapidly progressive ascending neuromuscular weakness.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/d4T.html**).

Pediatric Experience: Stavudine has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs. Data from multiple pediatric studies of stavudine alone or in combination with other antiretrovirals demonstrate that stavudine appears safe and is associated with clinical and virologic response *[1-11]* In resource-limited countries, stavudine is frequently a component of initial HAART therapy in children in combination with nevirapine or efavirenz, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 count and complete viral suppression in 50%–80% of treatment-naïve children *[12-15]*.

Early initiation of triple therapy with stavudine, didanosine, and nelfinavir was evaluated in 20 infants starting therapy at <3 months of age (median age at initiation, 2.5 months) *[1]*. Therapy was generally well tolerated; 7 infants (35%) experienced 11 events considered possibly related to study drugs, although only 3 such events (rash, diarrhea, and neutropenia) required drug modification. At least 1 episode of Grade 1 hypertriglyceridemia was observed in 19 of 20 (95%) infants; 9 of 12 (75%) infants with cholesterol measured after baseline had at least 1 episode of Grade 1 hypercholesterolemia. However, no infant had Grade 2 or higher triglyceride or cholesterol concentrations. Seventy percent of infants had incomplete viral suppression, which was associated with genotypic resistance mutations in 6 (30%) of these infants. However, only 2 infants developed resistance mutations to stavudine, and 1 of these infants had pre-existing TAMs present at baseline. Stavudine has been used as a component of a second regimen after treatment failure or as a replacement for zidovudine if the patient develops anemia. In a Phase II comparison study of stavudine and zidovudine, they were largely comparable in terms of safety and tolerability, although neutropenia occurred significantly less often among children receiving stavudine *[6]*. Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving combination therapy *[16-17]*. In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest but significantly higher rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated with stavudine *[17]*. Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults *[4, 6]*. Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of stavudine. In a small pediatric study of stavudine in combination with didanosine, no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy *[5]*. In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children *[17]*. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly stavudine, in adults and children *[18-20]*. Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy with 9 demonstrating lipoatrophy *[10]*. Among 90 children receiving stavudine, lamivudine, and nevirapine or efavirenz, 65% developed lipodystrophy at 33 months *[21]*. Further research concerning body habitus changes associated with NRTI use in pediatric patients is ongoing. Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, including stavudine, alone or in combination *[22-23]*. The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available *[24]*. Many of these adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA demonstrated in fat, muscle, peripheral blood mononuclear cells, and other tissues *[22, 25-27]*. (For additional information on lactic acidosis see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**.)

Although the World Health Organization has chosen to limit the maximum dose of stavudine to 30 mg (WHO guidelines at www.who.int/hiv/art/ARTadultsaddendum.pdf), these guidelines support switching to another agent rather than lowering the dose of stavudine to reduce the risk of or to manage toxicity. This recommendation is based on the availability of alternative antiretroviral agents in the United States and concerns of some Panel members about suboptimal therapy with a lower dose of stavudine.

References

1. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
2. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
3. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
4. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics.* 1995;96(2 Pt 1 (Aug)):247-252.
5. Kline MW, Fletcher CV, Federici ME, et al. Combination therapy with stavudine and didanosine in children with advanced human immunodeficiency virus infection: pharmacokinetic properties, safety, and immunologic and virologic effects. *Pediatrics.* 1996;97(6 Pt 1):886-890.
6. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr.* 1998;132(3 Pt 1):543-546.
7. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.

8. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
9. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *Journal of the American Medical Association.* 2000;283(4):492-498.
10. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
11. Yogev R, Lee S, Wiznia A, et al. for the Pediatric AIDS Clinical Trials Group 338 Study Team. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(2):119-125.
12. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA.* 2007;298(16):1888-1899.
13. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics.* 2007;120(5):e1134-1140.
14. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;46(2):187-193.
15. Zhang F, Haberer JE, Zhao Y, et al. Chinese pediatric highly active antiretroviral therapy observational cohort: a 1-year analysis of clinical, immunologic, and virologic outcomes. *J Acquir Immune Defic Syndr.* 2007;46(5):594-598.
16. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
17. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.
18. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS.* 2002;16(18):2447-2454.
19. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS.* 2004;18(10):1443-1451.
20. Ene L, Goetghebuer T, Hainaut M, et al. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. *Eur J Pediatr.* 2007;166(1):13-21.
21. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
22. Haugaard SB, Andersen O, Pedersen SB, et al. Depleted skeletal muscle mitochondrial DNA, hyperlactatemia, and decreased oxidative capacity in HIV-infected patients on highly active antiretroviral therapy. *J Med Virol.* 2005;77(1):29-38.
23. Koh MT. Unrecognized near-fatal hyperlactatemia in an HIV-infected infant exposed to nucleoside reverse transcriptase inhibitors. *Int J Infect Dis.* 2007;11(1):85-86.
24. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
25. Blanco F, Garcia-Benayas T, Jose de la Cruz J, et al. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials.* 2003;4(1):11-19.
26. Cherry CL, Gahan ME, McArthur JC, et al. Exposure to dideoxynucleosides is reflected in lowered mitochondrial DNA in subcutaneous fat. *J Acquir Immune Defic Syndr.* 2002;30(3):271-277.
27. Sanchez-Conde M, de Mendoza C, Jimenez-Nacher I, et al. Reductions in stavudine dose might ameliorate mitochondrial-associated complications without compromising antiviral activity. *HIV Clin Trials.* 2005;6(4):197-202.

Tenofovir Disoproxil Fumarate (TDF, Viread)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablet: 300 mg

Combination tablets:

- *With emtricitabine (FTC)*: 200 mg FTC + 300 mg TDF (Truvada)
- *With FTC + efavirenz (EFV)*: 200 mg FTC + 600 mg EFV + 300 mg TDF (Atripla)

Dosing Recommendations

Neonate/Infant dose:

Not approved for use in neonates/infants.

Pediatric dose:

Not approved for use in children <12 years of age; only commercially available preparation is 300-mg tablet. Investigational dose of 8 mg/kg of body weight once daily in children <12 years of age provided a lower exposure than was observed in adults.

Adolescent (≥12 years and >35 kg) dose:

300 mg once daily

See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (Tanner stages 1 and 2).

Dosing Recommendations for Combination Formulations

Truvada

Adult dose:

1 tablet once daily

Atripla

Adult dose:

1 tablet once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

TDF in combination with didanosine (ddI)

ddI dose requires modification. See section on **ddI**.

TDF in combination with atazanavir (ATV)

Only ATV boosted with ritonavir (RTV) should be used in combination with TDF. See section on **ATV**.

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, Fanconi syndrome
- Decreased bone mineral density

Special Instructions

- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. It is recommended to administer Atripla on an empty stomach because it contains EFV.
- When coadministered, ddI delayed-release capsule formulation and TDF may be taken under fasted conditions or with a light meal.
- Screen patients for hepatitis B virus infection (HBV) prior to use of TDF. Severe acute exacerbation of HBV can occur when TDF is discontinued; monitor hepatic function for several months after therapy with TDF is stopped.

Metabolism

- Renal excretion.
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.
- Atripla (fixed-dose combination) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***):

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- *Other NRTIs:* Didanosine serum concentrations are increased when coadministered with tenofovir.
- *PIs:* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir coadministered with tenofovir is atazanavir 300 mg with ritonavir 100 mg and tenofovir 300 mg, all as a single daily dose with food. Atazanavir without ritonavir should not be coadministered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.

Major Toxicities:

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/TDF.html**).

Pediatric Experience: In a Phase I/II study of tenofovir for salvage therapy using an investigational 75-mg formulation in 18 heavily pretreated children and adolescents at the National Institutes of Health (NIH) *[1]*, the major toxicity attributable to tenofovir was a >6% decrease in bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) scan in 5 of 15 (33%) children evaluated at Week 48. Two of the 5 children discontinued tenofovir at 48 weeks as required by the protocol and experienced partial or complete recovery of BMD by 96 weeks *[2]*. Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years *[2-3]*. In a second study of 6 patients at NIH using the commercially available 300-mg formulation of tenofovir, 2 prepubertal children experienced >6% BMD decreases. One of the 2 children, the smallest child in the study, experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her antiretroviral therapy regimen. The child continued therapy without tenofovir and subsequently her BMD recovered *[4]* The data from both of these small studies suggest that tenofovir-related bone loss may be greater in less mature children (e.g., Tanner 1–2) than in those with more advanced development (Tanner ≥3), and other studies offer further support for this conclusion *[5-6]*.

It is also possible that the bone loss seen in the patients in the NIH studies *[1-4]* may have been associated with higher tenofovir exposures. All participants were treated with regimens that also contained ritonavir, which increases tenofovir exposure *[7-8]*. Although the median initial dose in the Phase I/II studies was 208 mg/m^2 (= 7.1 mg/kg), the administered dose varied from 161 to 256 mg/m^2 (3.7 to 10 mg/kg) *[1]*. Loss of bone mineral density at 48 weeks was associated with higher drug exposure (AUC) *[3]*. However, in this heavily pretreated cohort, the group with the best virologic response had statistically significantly higher AUC, suggesting that in salvage therapy tenofovir may have a relatively small therapeutic window, especially in children in Tanner stages 1–2.

In contrast to the NIH studies, an Italian study showed no effect of tenofovir on BMD in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz *[9]*. The different results may be explained by different patient populations, differences in concurrent medication use, and tenofovir dosing. The patients in the Italian study *[9-11]* included older participants (up to age 18 years), had greater height and weight *z* scores, and the majority were in middle to late puberty or postpubertal. The NIH study involved heavily treatment experienced patients in need of salvage therapy while the Italian study evaluated BMD in a potentially healthier population of patients who were required to have long-lasting viral suppression prior to the switch in therapy. Finally, because the patients in the Italian study received tenofovir in the absence of ritonavir and were administered fractions of tenofovir pills to provide lower doses, the tenofovir concentrations experienced by the Italian patients may have been lower than those seen in the NIH patients. No BMD studies have been reported in treatment-naïve children who initiate therapy with tenofovir.

No significant renal disease was seen with tenofovir therapy in either of the 2 small NIH studies or in the Italian study. In 6/159 (3.7%) children with HIV-1 treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland, renal toxicity leading to discontinuation of tenofovir was reported *[12]*. All 6 of those patients were taking didanosine and lopinavir/ritonavir in addition to tenofovir, and the interaction of didanosine and tenofovir *[13]* or the boosting of tenofovir exposure by concurrent use of lopinavir/ritonavir *[7]* may have caused this toxicity. Possible tenofovir-associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance, and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including lopinavir/ritonavir and didanosine for 1 year *[14]*, and irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine *[15]*. Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 12 of 44 (27%) children treated with tenofovir

compared with 2 of 48 (4%) children not treated with tenofovir *[16]*. An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing combination antiretroviral therapy *[17]*. However, no significant decrease in calculated glomerular filtration rate was found in 27 HIV-infected children treated with tenofovir for 96 weeks *[10]*. Lipid profiles improved significantly after the switch from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz *[11]*.

The NIH study, using a 75-mg tablet formulation of tenofovir in treatment-experienced children and adolescents 6–18 years of age, showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and C_{max} that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg *[1, 18]*. Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure *[1]*. Steady-state tenofovir exposures were higher but still less than those seen in adults and may reflect the concomitant treatment with ritonavir, which boosts tenofovir plasma concentrations. Lower than anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir *[19]*. The clinical impact of these low drug exposures is unknown, but in the NIH study, lower single-dose and steady-state AUC were associated with inferior virologic outcome *[3]*. The CHIPS cohort used a target dose of 8 mg/kg, but 18% were dosed at >120% of the target and 37% at less than 80%.

In the Italian study, which only enrolled patients with undetectable viral load on current therapy, all HIV-infected children remained clinically stable and virologically suppressed after the change to a tenofovir-containing regimen *[11]*. In the NIH "salvage" study, plasma HIV RNA concentrations ($\log_{10}$ copies/mL) decreased from a median pretreatment concentration of 5.4 $\log_{10}$ copies/mL to 4.21 $\log_{10}$ copies/mL after 48 weeks of therapy *[3]*. HIV RNA was <400 copies/mL in 6/16 (37.5%) participants and <50 copies/mL in 4/16 (25%) participants at 48 weeks. In the CHIPS cohort 115 patients had outcome data available *[12]*. Viral load decreased to <50 copies/mL at 12 months in 38% of patients starting tenofovir for the first time; in 50% on first-line therapy; 39% of those on second-line therapy; and 13% of patients on third-line or greater therapy *[12]*.

In March 2010, the FDA approved the use of tenofovir in adolescents ≥12 years of age and weighing ≥35 kg based upon data from Gilead study 321, a randomized, placebo-controlled trial of tenofovir or placebo plus an optimized background regimen in 87 treatment-experienced adolescents between 12 and <18 years of age in Brazil and Panama *[20-21]*. No difference in viral load response was seen between the 2 groups. Subgroup analyses suggest this lack of response may have been due to imbalances in viral susceptibility to the optimized background regimens between the 2 groups. Importantly, impaired bone accrual was seen in the tenofovir group, manifest by declining BMD *z* scores over 48 and 96 weeks. In addition, 6 of 33 (18%) participants in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with only 1 of 33 (3%) participants in the placebo arm *[20-21]*. Limited pharmacokinetic data were reported from 8 participants and suggested that tenofovir exposures were higher than those seen in the NIH study, but no data on correlation of tenofovir exposure with BMD loss were provided.

Given this potential for BMD loss, some experts recommend obtaining a DXA prior to the initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner stages 1 and 2). However, in view of the potential cost and difficulty in obtaining pediatric DXA in some settings, other experts try to avoid using tenofovir in prepubertal patients and those in early puberty, especially for initial therapy. Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in adolescence is concerning and favors judicious use of tenofovir in this age group. There is still an urgent need for more research to develop appropriate pediatric formulations and to identify the safest uses of tenofovir in children and adolescents.

An investigational liquid formulation has been studied in children 2–8 years of age; a tenofovir dose of 8 mg/kg resulted in tenofovir exposure similar to that observed in adults receiving a tenofovir dose of 300 mg, but this formulation had poor palatability and was not developed further *[22]*. A powder formulation is also under investigation. An investigational dose of 8 mg/kg of body weight once daily in children <12 years of age provided a lower exposure than was observed in adults, and the FDA has recommended that a higher dose be evaluated in this age group *[21]*.

References

1. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):124-129.

2. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.
3. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics.* 2005;116(6):e846-854.
4. Purdy JB, Gafni RI, Reynolds JC, et al. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr.* 2008;152(4):582-584.
5. Jacobson D, Dimeglio L, Hazra R, et al. Clinical determinants of bone mineral density in perinatally HIV-infected children. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 911.
6. Thomas V, Purdy J, Reynolds J, et al. Bone mineral density in adolescents infected with HIV perinatally or childhood: Data from the NIH intramural program. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 912.
7. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther.* 2008;83(2):265-272.
8. Kearney BP, Mathias A, Mittan A, et al. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr.* 2006;43(3):278-283.
9. Giacomet V, Mora S, Martelli L, et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40(4):448-450.
10. Vigano A, Zuccotti GV, Martelli L, et al. Renal safety of tenofovir in HIV-infected children: a prospective, 96-week longitudinal study. *Clin Drug Investig.* 2007;27(8):573-581.
11. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther.* 2005;10(8):917-924.
12. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J.* 2009;28(3):204-209.
13. Crane HM, Kestenbaum B, Harrington RD, et al. Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir. *AIDS.* 2007;21(11):1431-1439.
14. Hussain S, Khayat A, Tolaymat A, et al. Nephrotoxicity in a child with perinatal HIV on tenofovir, didanosine and lopinavir/ritonavir. *Pediatr Nephrol.* 2006;21(7):1034-1036.
15. Wood SM, Shah SS, Steenhoff AP, et al. Tenofovir-associated nephrotoxicity in two HIV-infected adolescent males. *AIDS Patient Care STDS.* 2009;23(1):1-4.
16. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J.* 2007;26(10):949-951.
17. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J.* 2009;28(7):619-625.
18. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother.* 2001;45(10):2733-2739.
19. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2008;52(2):631-637.
20. TDF FDA label. 2010; http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021356s033lbl.pdf.
21. Food and Drug Administration (FDA). FDA clinical review.
22. Kearney B, Abadi J, Rosenberg M, et al. Pharmacokinetics of tenofovir DF oral suspension in HIV-1-infected children between 2 and 8 years of age. 11th Conference on Retroviruses and Opportunistic Infections; Feb 8-11, 2004; San Francisco, CA. Abstract 935.

Zidovudine (ZDV, AZT, Retrovir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg
Tablets: 300 mg
Syrup: 10 mg/mL
Concentrate for injection/for intravenous infusion: 10 mg/mL
Generic: ZDV capsules, tablets, and solution are approved by the FDA for manufacture and distribution in the United States.
Combination tablets:

- *With lamivudine (3TC)*: 300 mg ZDV + 150 mg 3TC (Combivir)
- *With 3TC + abacavir (ABC)*: 300 mg ZDV + 150 mg 3TC + 300 mg ABC (Trizivir)

Dosing Recommendations

Premature infant dose for prevention of transmission or treatment (standard neonate dose may be excessive in premature infants):
1.5 mg/kg of body weight (intravenous) or 2 mg/kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age)

Neonate/Infant dose (<6 weeks) for prevention of transmission or treatment:
Oral: 2 mg/kg of body weight every 6 hours
Intravenous: 1.5 mg/kg of body weight every 6 hours

Pediatric dose (6 weeks to <18 years):
Body surface area dosing:
Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours

Weight-based dosing:

Body Weight	Twice-Daily Dosing*
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

*Three times daily dosing is approved but rarely used in clinical practice.

Adolescent (≥18 years)/Adult dose:
200 mg three times a day or 300 mg twice daily

Dosing Recommendations for Combination Formulations

Combivir
Adolescent (weight ≥30 kg)/Adult dose:
1 tablet twice daily

Trizivir
Adolescent (weight ≥40 kg)/Adult dose:
1 tablet twice daily

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- GI intolerance, headache, insomnia, asthenia
- Lactic acidosis with hepatic steatosis

Special Instructions

- Can be given without regard to food.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or transfusion may be necessary in some patients.

Metabolism

- Metabolized to AZT glucuronide (GAZT), which is renally excreted.
- Dosage adjustment required in renal insufficiency.
- Decreased dosing may be required in patients with hepatic impairment.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)**:**

- *Other NRTIs:* Should not be administered in combination with stavudine due to virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* May increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Use should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia. Headache, malaise, nausea, vomiting, and anorexia.
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ZDV.html**).

Pediatric Experience: Zidovudine was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for treatment of HIV infection. Data from multiple pediatric studies of zidovudine alone or in combination with other antiretrovirals demonstrate that zidovudine appears safe and is associated with clinical improvement and virologic and immunologic effects *[1-16]*.

Perinatal trial PACTG 076 established that a zidovudine prophylactic regimen given during pregnancy, labor, and to the newborn reduced the risk of perinatal HIV transmission by nearly 70% *[17]*. Recommended neonatal zidovudine dosing for prevention of mother-to-child transmission of HIV is 2 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours for those unable to receive oral dosing. Although not FDA approved, twice-daily dosing (4 mg/kg every 12 hours) is sometimes prescribed when concerns about adherence exist, but the efficacy of this approach for prevention of mother-to-child transmission has not been evaluated. Pharmacokinetic studies, such as PACTG 331, have shown that dose adjustments are necessary for premature infants due to decreased zidovudine clearance compared with term newborns of similar postnatal ages *[2, 6]*. Resistance mutations were shown to be present in 5 of 17 (29%) newborns born to mothers who received zidovudine during pregnancy *[18]*.

Overall, zidovudine pharmacokinetics in pediatric patients >3 months of age are similar to those in adult patients. The manufacturer's recommended oral dose in pediatric patients 6 weeks to 12 years of age is 160 mg per meter^2 of body surface area every 8 hours or 240 mg per meter^2 of body surface area every 12 hours, in combination with other antiretroviral agents, although the recommended dose for adults is 300 mg twice daily. Recently, weight band dosing has also been approved *[19]*. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing is not recommended because of low intracellular zidovudine triphosphate concentrations seen with 600-mg once-daily dosing in adolescents *[20]*. Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease *[1]*.

References

1. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med.* 1989;110(4):279-285.
2. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47-52.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med.* 1997;336(24):1704-1712.
5. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
6. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clin Pharmacokinet.* 2002;41(14):1115-1133.
7. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
8. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med.* 1991;324(15):1018-1025.
9. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
10. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.
11. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
12. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
13. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
14. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.
15. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
16. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
17. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994;331(18):1173-1180.
18. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J.* 2005;24(6):503-509.
19. World Health Organization (WHO). Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: Report of the WHO paediatric antiretroviral working group. 2008; http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.
20. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522.

NON-NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Efavirenz (EFV, Sustiva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 50 mg and 200 mg
Tablets: 600 mg
Combination tablets:
- *with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)*:
  200 mg FTC + 300 mg TDF + 600 mg EFV (Atripla)

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Children <3 years of age:
There are currently no data available on the appropriate dosage for children <3 years of age.

Children ≥3 years and ≥10 kg:
Administer EFV once daily:

Weight (kg)	EFV dose (mg)*
10–<15	200
15–<20	250
20–<25	300
25–<32.5	350
32.5–<40	400
≥40	600

***** The dose in mg could be dispensed in any combination of capsule strengths; dose represents the maximum recommended EFV dose for each weight band.

Adolescent (≥40 kg)/Adult dose:
600 mg once daily

Dosing Recommendations for Combination Formulations

Atripla
Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.

Adult dose:
One tablet once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

Atazanavir (ATV), **fosamprenavir (FPV)**, **indinavir (IDV)**, **lopinavir/ritonavir (LPV/r)**, and **maraviroc (MVC)** used in combination with EFV may require dosage adjustment or addition of RTV. See appropriate drug section.

Selected Adverse Events

- Rash
- Central nervous system symptoms
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Teratogenic
- Lipohypertrophy

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. The relative bioavailability of EFV was increased by 50% (range 11%–126%) following a high fat meal. Because there is no information on the safety of EFV when given above the recommended dose, avoid administration with a high fat meal due to the potential for increased absorption.
- Administer Atripla on an empty stomach.
- Capsules may be opened and added to liquids or small amounts of food.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.

Metabolism

- Metabolized by cytochrome P450, 2B6, and 3A4. CYP 3A4 inducer/inhibitor (more inducer than inhibitor).
- Dosing of EFV in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or in patients on dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Mixed inducer/inhibitor of cytochrome P450 3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. Central nervous system abnormalities (e.g., somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) primarily reported in adults.
- *Rare*: In cynomolgus monkeys, prenatal efavirenz exposure has been associated with central nervous system congenital abnormalities in infant monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe central nervous system defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). Efavirenz use in the first trimester of pregnancy should be avoided. Women of childbearing potential should undergo pregnancy testing and be counseled about the risk of efavirenz to the fetus and need to avoid pregnancy before initiating and during efavirenz therapy.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/EFV.html**).

Pediatric Experience: Efavirenz has been studied in HIV-infected children in combinations of efavirenz plus NRTIs or efavirenz plus NRTIs plus a PI (nelfinavir or lopinavir/ritonavir) *[1-17]*. An open label study (PACTG 382) of efavirenz combined with nelfinavir and 1 or 2 NRTIs was performed in 57 NNRTI- and PI-naïve pediatric patients, some as young as 3 years of age *[11]*. In an intent-to-treat analysis, 76% of children had plasma HIV RNA concentrations <400 copies/mL and 63% had HIV RNA concentrations <50 copies/mL at 48 weeks of therapy. The median times to achieve those concentrations were 4 and 20 weeks, respectively. Therefore, children with detectable HIV RNA (>50 copies/mL by the ultra-sensitive RNA assay) after 1 month of therapy continued to accrue some virologic benefit through 5 months of treatment with this regimen *[10]*. Long-term virologic suppression with once-daily efavirenz therapy in combination with emtricitabine and didanosine was reported in 37 treatment-naïve children, 3–18 years of age, participating in PACTG 1021 *[8]*. Eighty-five percent of subjects were able to achieve HIV-RNA <400 copies/mL and 72% maintained HIV-RNA suppression <50 copies/mL through 96 weeks of therapy.

A study of a liquid formulation of efavirenz in 19 HIV-infected children 3–9 years of age has been reported *[12]*. A 20% higher dose of efavirenz liquid formulation resulted in pharmacokinetic AUC values that were similar to those observed with efavirenz capsules. Limited pharmacokinetic data in children <3 years of age or who weigh <13 kg have shown that it is difficult to achieve target trough concentrations in this age group even with very high (>30 mg/kg) doses of this investigational liquid formulation *[18]*. Thus, efavirenz is not recommended for use in children <3 years of age at this time and no liquid formulation is commercially available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large between patient variability in efavirenz exposure. CYP 2B6 is the primary enyzme for efavirenz metabolism and pediatric patients with the 516 T/T or G/T genotype have reduced metabolism and higher efavirenz levels compared with those with the G/G genotype *[19-20]*. Additional variant CYP 2B6 alleles and variant CYP 2A6 alleles have been found to influence efavirenz concentrations in adults *[21-22]*.

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations >1 mcg/mL in adults *[23]*. Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA ≤400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL) *[3]*. In a West African pediatric study, ANRS 12103, early reduction in viral load (12 weeks) was greater in children with efavirenz C_{min} >1.1 mcg/mL or AUC >51 mcg*h/mL *[24]*. Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal *[19, 24-25]*, so that some experts recommend therapeutic drug monitoring when using efavirenz and possibly using higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In 1 study that adjusted the efavirenz

dose in response to measurement of the AUC, the administered efavirenz dose median was 13 mg/kg (367 mg/m^2) and the range was from 3 to 23 mg/kg (69 to 559 mg/m^2) *[3]*. A pharmacokinetic study in 20 children age 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m^2 twice daily plus efavirenz 350 mg/m^2 once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than pharmacokinetic targets, and the authors recommend that higher doses of efavirenz might be needed when these drugs are used together *[16]*. Therapeutic drug monitoring might be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. In adults, a central nervous system (CNS) complex of confusion, agitation, sleep disturbance, nightmares, hallucinations, or other symptoms has been reported in >50% of patients *[26]*. These symptoms usually occur early in treatment and rarely require drug discontinuation but sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in patients with higher concentrations *[23, 27-30]*. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies *[11]* and in 30% of children with efavirenz concentrations >4 mcg/mL *[20]*. The principal side effect of efavirenz in children is rash, which was seen in up to 40% of children, compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically in the first 2 weeks of treatment *[11]*. Although severe rash and Stevens-Johnson syndrome have been reported, this is rare. Other reported adverse events in adults and children include diarrhea, nausea, and increased transaminases including liver failure *[31]*. There are insufficient data to recommend substituting nevirapine for efavirenz following either rash or hepatotoxicity *[32]*.

Efavirenz should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity *[33]*. See ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** *[34]*. Many clinicians choose alternative drugs for use in sexually active adolescent women in whom contraception use is sometimes erratic and the risk of unintended pregnancy is high.

References

1. Brundage RC, Yong FH, Fenton T, et al. Intrapatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. *Antimicrob Agents Chemother.* 2004;48(3):979-984.
2. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
3. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306.
4. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
5. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res.* 2005;10(12):503-508.
6. King JR, Yogev R, Aldrovandi G, et al. Pharmacokinetics of antiretrovirals administered to HIV-infected children via gastrostomy tube. *HIV Clin Trials.* 2004;5(5):288-293.
7. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics.* 2003;111(3):e275-281.
8. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
9. Scherpbier HJ, Bekker V, Pajkrt D, et al. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics.* 2007;119(3):e705-715.
10. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis.* 2000;182(6):1769-1773.
11. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
12. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
13. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS.* 2001;15(2):241-243.

14. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther.* 2005;10(8):917-924.
15. Wintergerst U, Engelhorn C, Kurowski M, et al. Pharmacokinetic interaction of amprenavir in combination with efavirenz or delavirdine in HIV-infected children. *AIDS.* 2000;14(12):1866-1868.
16. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2009;28(2):159-161.
17. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
18. Capparelli E, Rochon-Duck M, Robbins B, et al. Age-related pharmacokinetics of efavirenz solution. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montréal, Canada. Abstract 884.
19. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr.* 2007;45(3):280-285.
20. Puthanakit T, Tanpaiboon P, Aurpibul L, et al. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther.* 2009;14(3):315-320.
21. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics.* 2009;19(4):300-309.
22. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther.* 2009;85(5):485-494.
23. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS.* 2001;15(1):71-75.
24. Hirt D, Urien S, Olivier M, et al. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? *Antimicrob Agents Chemother.* 2009;53(10):4407-4413.
25. Ren Y, Nuttall JJ, Egbers C, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. *J Acquir Immune Defic Syndr.* 2007;45(2):133-136.
26. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
27. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648-1653.
28. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care.* 2006;4(1).
29. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS.* 2002;16(9):1201-1215.
30. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother.* 2008;61(6):1336-1339.
31. Turkova A, Ball C, Gilmour-White S, et al. A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation. *J Antimicrob Chemother.* 2009;63(3):623-625.
32. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis.* 2007;7(11):733-738.
33. Saitoh A, Hull AD, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol.* 2005;25(8):555-556.
34. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.

Etravirine (ETR, Intelence, TMC 125)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 100 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children.

Adult dose (ARV-experienced patients):
200 mg (two 100 mg tablets) twice daily following a meal

Selected Adverse Events

- Nausea
- Rash including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure

Special Instructions

- Always administer ETR following a meal; area under the curve (AUC) is decreased by about 50% when taken on an empty stomach.
- Tablets are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow tablets may disperse the tablets in a small amount of water. Once dispersed, instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times and each of the rinses completely swallowed to ensure that the entire dose is consumed.
- Dosing of ETR in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of ETR in patients with renal impairment: No dose adjustments are required in patients with renal impairment.

Metabolism

- Metabolism by cytochrome P450: inducer of CYP3A4 and inhibitor of CYP2C9, CYP2C19. Substrate for CYP3A4, 2C9, and 2C19. Also inhibitor of P-glycoprotein.
- Multiple drug interactions (see below).

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Etravirine is an inducer of CYP3A4; an inhibitor of CYP2C9 and CPY2C19; and a substrate for 3A4, 2C9, and 2C19. Etravirine is also an inhibitor of P-glycoprotein.
- There are multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Etravirine should not be coadministered with the following antiretrovirals: tipranavir/ritonavir, fosamprenavir/ritonavir, amprenavir/ritonavir, ritonavir, unboosted PIs, nevirapine, or efavirenz.

Major Toxicities:

- *More common:* Nausea, diarrhea, mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common:* Severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and

appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ETR.html**).

Pediatric Experience: The pharmacokinetics, safety, and efficacy of etravirine in pediatric patients have not been established. There is limited pediatric experience and pediatric trials are under way. Recently reported are the results of a Phase I dose finding study involving 21 children with virologic suppression on a stable lopinavir/ritonavir-containing regimen *[1]*. Etravirine therapy was added for 1 week and pharmacokinetic sampling and analysis were performed. The findings from this trial were used to determine the dose in the Phase II trial in pediatric patients that is currently under way. At this time data are insufficient to recommend a pediatric dose and further studies are warranted to determine the pharmacokinetics, safety, and efficacy of etravirine in children.

Recently reported was an analysis of genotypic and phenotypic HIV resistance profiles in 35 children from a Ugandan clinic with clinical failure of a first-line regimen containing an NNRTI other than etravirine *[2]*. Reduced etravirine susceptibility (fold-change >2.9) was found based on phenotypic analysis in 35% of samples.

References

1. Konigs C, Feiterna-Sperling C, Exposito S, et al. Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract S-167.
2. Kekitiinwa A, Friedman D, Coakley E, et al. Profiling etravirine resistance in Ugandan children with extended failure of a NNRTI-inclusive regimen as first-line ART. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 891.

Nevirapine (NVP, Viramune)

For more information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Tablets: 200 mg
Suspension: 10 mg/mL

Dosing Recommendations

Neonate/Infant dose (<14 days):
When used for prophylaxis of mother-to-child transmission of HIV see **Perinatal Guidelines**.[†]
Treatment dose not defined for infants ≤14 days of age.

Pediatric dose (≥15 days):
(See note below about initiation of therapy.)

<8 years:
200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

≥8 years: 120–150 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m^2 dosage as the child grows, as long as there are no untoward effects.

NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased clearance of the drug. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/Adult dose:
200 mg twice daily

Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

NVP in combination with lopinavir/ritonavir (LPV/r)
A higher dose of LPV/r may be needed. See **LPV/r** section.

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- Can be given without regard to food.
- May be administered concurrently with didanosine (ddI).
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves (see *Major Toxicities*).
- If NVP dosing is interrupted for >7 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.
- Shake suspension well and store at room temperature.

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- Dosing of NVP in patients with renal failure receiving hemodialysis: An additional dose of NVP should be given following dialysis.
- Dosing of NVP in patients with hepatic impairment: NVP should not be administered to patients with moderate or severe hepatic impairment.

[†] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, with a 1.5–2-fold increase in clearance. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be coadministered to patients receiving atazanavir (with or without ritonavir).

Major Toxicities:

(*Note:* These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.)

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against the patient's overall ability to tolerate the regimen and the current antiviral response. Nevirapine should be discontinued immediately and not restarted in patients who develop severe rash, a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash accompanied by elevated hepatic transaminases.
- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy; may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Hypersensitivity reactions have been reported, including but not limited to severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/NVP.html**).

Pediatric Experience: Nevirapine has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI *[1-9]*. Combination therapy with nevirapine, zidovudine, and didanosine in young infected infants was associated with sustained viral suppression in a small number of children *[6]*. A description of 15 infants initiating nevirapine-based antiretroviral treatment younger than 66 days of age in Belgium reported that complete viral suppression (<400 copies/mL) was achieved in 11 (73%) infants *[10]*. A larger study, PACTG 356, treated infants and young children with 3 different nevirapine-containing regimens: zidovudine/lamivudine/nevirapine, zidovudine/lamivudine/abacavir/nevirapine, or zidovudine/lamivudine/nevirapine/nelfinavir *[4]*. Twenty-four percent of 17 infants treated with the 3-drug regimen had viral suppression to <400 copies/mL HIV RNA, compared with 10 of 17 (41%) and 15 of 18 (83%), respectively, of infants treated with 4 drugs. Children who started therapy younger than 3 months of age had a better virologic outcome compared with children who started at an older age (3.5–24 months). PACTG 377 randomized 181 PI- and NNRTI-naïve mild to moderately immune suppressed children to 1 of 4 combination treatment regimens. All of the regimens contained stavudine and a PI (either ritonavir or nelfinavir); 3 of the 4 regimens also included nevirapine as part of combination therapy. Children in the nevirapine-containing arms experienced moderate or worse skin rash more frequently than did children not receiving nevirapine. Those children receiving a 4-drug regimen containing both nevirapine and a PI had a significantly greater increase in CD4 cell count from baseline to Week 24 than children receiving other regimens *[9]*. A study of 212 children in Cambodia treated with NNRTI-based combination therapy (82% nevirapine and 18% efavirenz) reported 156 of 212 children (73.6%) having undetectable viral load (<400 copies/mL) after 12 months of treatment. Only 2 children switched regimens due to intolerability of nevirapine *[1]*. In PACTG 403, 41 children with prior NRTI experience were randomized to receive stavudine/nelfinavir/nevirapine or didanosine/nelfinavir/ritonavir. After 48 weeks of therapy, only 28% (5/18) of those still on the nevirapine-inclusive regimen had viral suppression to <400 copies/mL compared with 65% (11/17) of children on the ritonavir-based treatment. The changes in CD4 percentage and the rates of toxicities were similar for both regimens. Three children developed nevirapine-related rashes leading to discontinuation of study treatment *[2]*.

In infants and children previously exposed to single-dose nevirapine for prevention of mother-to-child transmission (PMTCT), nevirapine-based antiretroviral therapy is less likely than lopinavir/ritonavir-based ART to control virus load. In a small, nonrandomized study in Botswana, 6-month virologic and immunologic responses were compared between 15 SD nevirapine-exposed and 15 -unexposed infants who initiated nevirapine-based antiretroviral treatment at a mean age of 8 months (range 2–33 months) in follow-up from a PMTCT study *[11]*. Only 34% of those with a history of exposure had an undetectable viral load (<400 copies/mL) compared with 91% of the unexposed cohort. CD4 percentage was also significantly lower in the exposed group compared with the unexposed group, 23% versus 31%, respectively. In contrast, in a study in Uganda, in which children with SD nevirapine exposure started nevirapine-based treatment at an older age of 1.6 years, there was no difference in response to therapy between children with and without prior SD nevirapine exposure *[12]*. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure [VF] defined as <1 log decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/lopinavir/ritonavir arm, p = 0.0009. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, p = 0.027. Based on these findings the Data and Safety Monitoring Board (DSMB) recommended discontinuing enrollment in this cohort. Enrollment into the comparison study of nevirapine versus lopinavir/ritonavir in children 6–36 months of age not previously exposed to nevirapine is ongoing *[13]*.

Body surface area has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid underdosing of nevirapine because a single point mutation may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children >8 years of age. *[6-7]*. Because of this, it is recommended that dosing for children younger than 8 years of age be 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children 8 years or older, the recommended dose is 120 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. When adjusting the dose in a growing child, the milligram dose need not be decreased (from 200 mg/m^2 to 120 mg/m^2) as the child reaches 8 years; rather, the milligram dose is left static as long as there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m^2 dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum of 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

References

1. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics.* 2007;120(5):e1134-1140.
2. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
3. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
4. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
5. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis.* 1996;174(4):713-721.
6. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
7. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet.* 2000;39(4):281-293.
8. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS.* 2003;17(11):1639-1647.
9. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.

10. Van der Linden D, Hainaut M, Goetghebuer T, et al. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J.* 2007;26(4):359-361.
11. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
12. Barlow-Mosha L, Ajunua P, Mubiru M, et al. Early effectiveness of a NVP-based HAART regimen among HIV-infected children with and without prior single-dose NVP exposure. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Abstract 583.
13. Palumbo P, Violari A, Lindsey J, et al. Nevirapine (NVP) vs lopinavir-ritonavir (LPV/r)-based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV-infected infants: preliminary results from the IMPAACT P1060 trial. Paper presented at: 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPEB12.

PROTEASE INHIBITORS

Atazanavir (ATV, Reyataz)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg, 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants. ATV should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
There are insufficient data to recommend dosing in all children younger than 6 years of age or for treatment-experienced children weighing less than 25 kg.

For children 6–18 years of age:

Weight (kg)	Once-Daily Dose*
Treatment-Naïve ** Children Only	
15 to <25 kg	ATV 150 mg + RTV 80 mg, both once daily with food
Both Treatment-Naïve and Treatment-Experienced Children	
25 to <32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32 to <39 kg	ATV 250 mg + RTV 100 mg, both once daily with food
≥39 kg	ATV 300 mg + RTV 100 mg, both once daily with food

*Higher doses than those currently recommended may be required for some patients. See discussion under pediatric experience.
**There are insufficient data to recommend this dose in treatment-experienced children weighing less than 25 kg.

For treatment-naive pediatric patients who do not tolerate ritonavir (RTV): **Atazanavir boosted with RTV is preferred for children and adolescents.** Current FDA-approved prescribing information does not recommend unboosted ATV in children younger than 13 years of age. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see pediatric experience section).

Adolescent (≥16–21 years)/Adult dose:
Antiretroviral-naïve patients:
ATV 300 mg + RTV 100 mg **or** ATV 400 mg once daily with food

Antiretroviral-experienced patients:
ATV 300 mg + RTV 100 mg, both once daily with food

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged PR interval, first degree symptomatic AV block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis

Special Instructions

- Administer ATV with food to enhance absorption.
- Unboosted ATV does not appear to increase cholesterol or triglyceride levels. However, ATV boosted with RTV may be associated with lipid abnormalities.
- Because ATV can prolong the electrocardiogram PR interval, use with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH and when administered with medications that alter gastric pH, special dosing information is indicated. When administered with buffered didanosine (ddI) formulations or antacids, ATV should be taken at least 2 hours before or 1 hour after antacid or ddI administration.
- Individuals with HBV or HCV infections and individuals with marked elevations in transaminases prior to treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of CYP3A4 and an inhibitor of CYP1A2, CYP2C9, and UGT1A1.
- Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for adjustment of dosage in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs	
ATV in combination with efavirenz (EFV) in therapy-naïve patients only **Adult dose:** ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily but at separate times Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure. ***ATV in combination with tenofovir (TDF)*** **Adult dose:** ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents****.)*:

- *Metabolism*: Atazanavir is both a substrate and an inhibitor of the CYP3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *NRTIs*: Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *NNRTIs*: Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in treatment-experienced patients but may be used in treatment-naïve adults with atazanavir 400 mg plus ritonavir boosting.
- *Absorption*: Atazanavir absorption is dependent on low gastric pH and when administered with medications that alter gastric pH, special dosing information is indicated. No information is available in children when dosing atazanavir with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton pump inhibitors in adults are as follows:

- *Antacids*: Antacids and buffered medications (including buffered didanosine formulations) decrease atazanavir concentrations if administered at the same time; atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted atazanavir in treatment-naïve patients)*: H2-receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2-receptor antagonist (no single dose should exceed a dose comparable to famotidine 20 mg and total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-Receptor Antagonists (boosted atazanavir in treatment-naïve or -experienced patients)*: H2-receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption. Dose recommendations for H2-receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily (treatment-naïve patients) or a ≤20-mg dose equivalent of famotidine twice daily (treatment-experienced patients). Dose (ATV 300 mg + RTV 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2-receptor antagonist.
- *H2-Receptor Antagonists (boosted atazanavir with tenofovir)*: In treatment-experienced patients, if tenofovir is used with H2-receptor antagonists, an increased dose of atazanavir should be given: 400 mg ATV + 100 mg RTV + 300 mg TDF.
- *Proton-pump Inhibitors:* Coadministration of atazanavir with proton-pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and decrease therapeutic effect. Dose recommendations for therapy-naïve patients are

≤20-mg dose equivalent of omeprazole taken approximately 12 hours prior to boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with proton-pump inhibitors is not recommended in treatment-experienced patients.

Major Toxicities:

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.
- *Less common:* Prolongation of PR interval of electrocardiogram. Abnormalities in AV conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or C are at increased risk).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ATV.html**).

Pediatric Experience: IMPAACT/PACTG 1020A is an ongoing Phase II international trial of atazanavir with and without ritonavir in children 3 months to 19 years of age. In addition to capsules, a powder formulation of atazanavir is also under study. In this trial, atazanavir plasma concentration monitoring is used to guide therapy and establish optimum starting doses. Both ritonavir-boosted and -unboosted atazanavir regimens are used for treatment-naïve and -experienced patients. In the trial, protocol-defined AUC, C_{min}, and C_{max} targets were deliberately set at levels higher than those achieved in the early adult atazanavir trials to compensate for the wide interpatient variability in pharmacokinetics values seen in adults in those trials; the pharmacokinetic targets were the same for atazanavir given with and without ritonavir boosting. In IMPAACT/PACTG 1020A, dosing for each age cohort was targeted to achieve AUC ≥30 μg*hour/mL and C24 ≥60 ng/mL.

To date, the results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic targets, but only when used at higher doses of atazanavir (on a mg-per-kg body weight or mg-per-meter^2 body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children >6 and <13 years of age required atazanavir dosing of 520 mg per meter^2 of body surface area per day of atazanavir capsule formulation to achieve pharmacokinetic targets. For older adolescents, doses required were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents age >13 years required ATV dosing of 620 mg per meter^2 of body surface area per day *[1-2]*. In this study, the AUCs for the unboosted arms were similar in the ritonavir-boosted atazanavir groups but the C_{max} was higher and C_{min} lower for the unboosted arms. Median doses of atazanavir in mg/m^2 both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150ng/mL *[3]*. Higher target trough concentrations may be required in PI-experienced patients.

Summary of Dosing Information Obtained from IMPAACT/PACTG 1020A *[2]*

Age range (years)	Was ATV given with RTV boosting?	ATV median dose in mg/m^2*	ATV median dose in mg*
6–13 years	No	509	475
6–13 years	Yes	208	200
>13 years	No	620	900
>13 years	Yes	195	350

*Data satisfied protocol-defined AUC/pharmacokinetic parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. Therapeutic drug monitoring was used to determine patient-specific dosing in this trial.

A summary of the efficacy results from IMPAACT/PACTG 1020A is included in the prescribing information: In 99 patients (6 years to >18 years of age) treated with either boosted or unboosted atazanavir, the overall proportions of antiretroviral-naïve and -experienced patients with HIV RNA <50 copies/mL at Week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 and 116 cells/mm^3 in antiretroviral-

naïve patients and antiretroviral-experienced patients, respectively *[4]*. Overall, 11 of 129 (8.5%) patients enrolled had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (EKG) abnormalities were observed in a small number of patients: 1 patient had a Grade 3 QTC prolongation, 9 had Grade 2 PR or HR changes, and 3 had Grade 3 PR prolongations. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs *[5]*.

In a small single site study, 23 pediatric patients (median age 16) on combination antiretroviral therapy were switched to a once-daily ritonavir-boosted atazanavir (ATV/r)-containing regimen for virologic failure (12) or for treatment simplification (11) *[6]*. Twenty of the patients had previously received protease inhibitor-based regimens with the median number of 2 atazanavir mutations. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine; both drugs are known to have pharmacokinetic interactions with atazanavir. In this study, atazanavir plasma concentrations were measured at 12–15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients with previously undetectable viral loads experienced virologic failure and 6 of the 12 patients who previously had virologic failure achieved undetectable viral loads. This study provides further evidence of the large interpatient variability in atazanavir pharmacokinetics in children, the need for higher doses, and the potential benefit of therapeutic drug monitoring to ensure that adequate atazanavir concentrations are achieved.

References

1. Kiser J, Rutstein R, Aldrovandi G, et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25 2005; Boston, MA. Abstract 767.
2. Rutstein R, Samson P, Kiser J, et al. Atazanavir in HIV-infected children: The 1020a protocol. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections (CROI); February 27, 2007; Los Angeles, CA. Abstract 715.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
4. Bristol-Myers Squibb. Reyataz (atazanavir sulfate) package insert. Revised March 2008. www.reyataz.com.
5. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.
6. Macassa E, Delaugerre C, Teglas JP, et al. Change to a once-daily combination including boosted atazanavir in HIV-1-infected children. *Pediatr Infect Dis J.* 2006;25(9):809-814.

Darunavir (DRV, Prezista)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Dosing Recommendations

Darunavir should not be used without ritonavir (RTV).

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
DRV should not be used in pediatric patients <3 years of age.

3 to <6 years:
Safety and efficacy have not been established.

6 to <18 years and ≥20 kg:

Weight	Dose (both twice daily* with food)
≥20 to <30 kg	DRV 375 mg + RTV 50 mg (0.6 ml of 80 mg/ml)
≥30 to <40 kg	DRV 450 mg + RTV 60 mg (0.8 ml of 80 mg/ml)
≥40 kg	DRV 600 mg + RTV 100 mg

* Do not use once-daily dosing in pediatric patients.

Adolescent (age ≥18 years)/Adult dose (treatment naïve):
DRV 800 mg + RTV 100 mg, both once daily with food

Adolescent (age ≥18 years)/Adult dose (treatment experienced):
DRV 600 mg + RTV 100 mg, both twice daily with food

Selected Adverse Events

- Skin rash (DRV has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Hepatotoxicity
- Diarrhea
- Nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Administer DRV with food, which increases AUC and Cmax by 30%. Drug exposure is not significantly altered by the number of calories and fat content of the meal.
- DRV contains a sulfa moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store at room temperature (25ºC or 77ºF).

Metabolism

- CYP 3A4 inhibitor and substrate.
- Dosing in patients with hepatic impairment: DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with moderate renal impairment (CrCl 30–60 mL/min). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Darunavir is primarily metabolized by cytochrome P450 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. There is the potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome, have been reported. Fever and elevated hepatic transaminases have been reported. Lipid abnormalities.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (e.g., hepatitis B or hepatitis C virus coinfection, baseline elevation in transaminases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/DRV.html**).

Pediatric Experience: FDA approval for use in children 6 years of age and older was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric subjects age 6–<18 years and weighing ≥20 kg. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least 2 non-PI antiretroviral drugs *[1]*. This was a 2-part Phase II trial to evaluate the pharmacokinetics and tolerance of darunavir/ritonavir in children. In Part I, a weight-adjusted dose of darunavir 9–15 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with AUC_{24h} of 81% and C_{0h} of 91% of the corresponding adult pharmacokinetic (PK) parameters. A pediatric dose 20%–33% higher than the scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11–19 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily. This resulted in AUC_{24h} of 123,276 ng*h/ml (range 71,850–201,520) and C_{0h} of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation all patients were allowed to switch to ritonavir 100-mg capsules if desired to avoid the use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight band doses of darunavir/ritonavir were as follows: 375/50 mg twice daily for body weight 20 to <30kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. Note that 27 of the 80 participants in this portion of the study switched from the ritonavir liquid formulation to ritonavir 100-mg capsules. The 80 subjects had a median age of 14 (range 6 to <18 years), 71% were male, 54% white, 30% black, 9% Hispanic, and 8% other. The mean baseline plasma HIV-1 RNA was 4.64 $\log_{10}$ copies/mL, and the median baseline CD4 cell count was 330 cells/mm^3 (range: 6–1,505 cells/mm^3). Overall, 38% of pediatric subjects had baseline plasma HIV RNA ≥100,000 copies/mL, 79% had previous use of at least 1 NNRTI, and 96% had previously used at least 1 PI. The subjects had a median of 11 PI mutations. Only 6% of subjects discontinued the study before Week 48 (only 1 for an adverse event). The proportion of pediatric subjects with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 was 59% and 48%, respectively. The mean CD4 cell count increase from baseline was 110 cells/mm^3.

Although darunavir is approved for once-daily dosing in antiretroviral-naïve adults, it should not be used once daily in children because of more rapid clearance and absence of pediatric data.

References

1. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS.* 2009;23(15):2005-2013.

Fosamprenavir (FPV, Lexiva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral suspension: 50 mg/mL
Tablets: 700 mg FPV calcium

Dosing Recommendations

Neonate/Infant dose: Not approved for use in neonates/infants.

Pediatric dose (2–18 years of age): Dosing regimen depends on whether patient is antiretroviral naïve or antiretroviral experienced. Once-daily dosing is not recommended for pediatric patients.

Antiretroviral-naïve patients (2–5 years):
Unboosted (without ritonavir [RTV])
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily

Antiretroviral-naïve patients (≥6 years):
Unboosted (without RTV)
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily
or
Boosted with RTV
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily

Antiretroviral-experienced patients (≥6 years):
Boosted with RTV
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily

When administered without RTV, the adult regimen of FPV tablets (FPV 1,400 mg twice daily) can be used for patients weighing ≥47 kg **or** when administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Adolescent (>18 years)/Adult dose:
Dosing regimen depends on whether the patient is antiretroviral naïve or experienced.

Antiretroviral-naïve patients:
Unboosted (without RTV), twice-daily regimen
FPV 1,400 mg twice daily
Boosted with RTV, twice-daily regimen
FPV 700 mg + RTV 100 mg, both twice daily
Boosted with RTV, once-daily regimen
FPV 1,400 mg + RTV 200 mg, both once daily **or**
FPV 1,400 mg + RTV 100 mg, both once daily

Protease inhibitor-experienced patients:
FPV 700 mg + RTV 100 mg, both twice daily

Once-daily administration of FPV + RTV is not recommended in PI-experienced patients.

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Tablets can be taken with or without food. Adults should take the suspension without food. Pediatric patients can take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take FPV at least 1 hour before or after antacid or ddI use.
- FPV contains a sulfonamide. The potential for cross sensitivity between FPV and other drugs in the sulfonamide class is unknown. FPV should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well prior to use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as it is absorbed.
- APV is a cytochrome P450 3A4 inhibitor, inducer, and substrate.
- Dosage adjustment in patients with hepatic insufficiency is recommended.

Fosamprenavir (FPV, Lexiva)

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs	
FPV in combination with efavirenz (EFV) Only FPV boosted with RTV should be used in combination with EFV. **Adult dose:** *Twice-daily regimen* FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily *PI-naïve patients only, once-daily regimen* FPV 1,400 mg + RTV 300 mg + EFV 600 mg, all once daily ***FPV in combination with maraviroc (MVC)*** **Adult dose:** See **MVC** section for dosing of FPV with MVC.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/APV_FPV.html**).

Pediatric Experience: In June 2007, fosamprenavir suspension was approved for use in pediatric patients. The approval was based on two open label studies in pediatric patients 2–18 years of age *[1-2]*. Both studies enrolled treatment-experienced and treatment-naïve subjects. In one study, twice-daily dosing regimens (with or without ritonavir) were evaluated in combination with other antiretroviral agents. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count. In one trial, after 24 weeks 67% of PI-naïve subjects in the fosamprenavir group (age 2–5 years only) and 70% of PI-naïve subjects in the fosamprenavir/ritonavir group (age 5–18 years) but only 57% of PI-experienced subjects in the fosamprenavir/ritonavir group (age 5–18 years) achieved HIV RNA <400 copies/mL. Median increases in CD4 percent at Week 24 occurred in all groups and ranged from 4% to 8% *[2]*. In a second trial, once-daily fosamprenavir/ritonavir was studied. Following information about suboptimal response to once-daily dosing in treatment-experienced adults, pediatric patients were allowed to switch to twice-daily therapy; however, few patients (10 of 69) opted to switch to twice-daily therapy (median time to switch: 45 weeks). At 24 and 48 weeks of therapy, HIV RNA was <400 copies/mL in 66% and 47% among PI-naïve subjects, respectively, and 57% and 43% among PI-experienced subjects, respectively. Median increase in CD4 percent at Week 48 was 10% for PI-naïve and 5% for PI-experienced subjects *[1]*. These data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children and hence once-daily dosing is not recommended for pediatric patients. Toxicities from these trials included vomiting (3%–7%), diarrhea (3%–4%), and nausea (3%–4%).

A trial of pediatric patients taking the parent compound (amprenavir) demonstrated that the drug was relatively well tolerated with mild-to-moderate toxicity related mainly to the gastrointestinal system *[3]*.

References

1. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 719.
2. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 718.
3. Yogev R, Kovacs A, Chadwick EG, et al. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother*. 2005;49(1):336-341.

Indinavir (IDV, Crixivan)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.
Should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
Not approved for use in children.

Investigational dose:
500 mg/m^2 of body surface area every 8 hours

Adolescent/Adult dose:
800 mg every 8 hours

IDV in combination with ritonavir (RTV)
Adolescent/Adult dose:
800 mg IDV + 100 or 200 mg RTV every 12 hours

Selected Adverse Events

- Nephrolithiasis
- GI intolerance, nausea
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer on an empty stomach 1 hour before or 2 hours after a meal (or administer with a light meal). When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If coadministered with didanosine (ddI), give ≥1 hour apart on an empty stomach.
- Capsules are sensitive to moisture; store at room temperature (59–86ºF) in original container with desiccant.

Metabolism

- Cytochrome P450 3A4 inhibitor and substrate.
- Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg IDV every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritis, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits: cumulative frequency is higher in children (29%) than in adults (12.4%).
- *Less common (more severe):* Fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/IDV.html**).

Pediatric Experience: Indinavir has not been approved by the FDA for use in the pediatric population. It has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs in dosage ranges of 300–600 mg per

meter^2 of body surface area given every 8 hours *[1-16]*. Data in children indicate that a pediatric dose of 500–600 mg indinavir per meter^2 of body surface area given every 8 hours results in peak blood concentrations similar to those in adults; however, a significant proportion of children had trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults *[3, 10]*.

Ritonavir-boosted indinavir has also been studied in children. One study evaluated 500 mg indinavir per meter^2 of body surface area plus 100 mg ritonavir per meter^2 of body surface area twice daily in 4 children 1–10 years of age; in 1 child, this resulted in high concentrations of both drugs and was accompanied by symptoms of renal toxicity *[11]*. Another study evaluated the pharmacokinetics of 400 mg indinavir per meter^2 of body surface area plus 125 mg ritonavir per meter^2 of body surface area twice daily in 14 children; this dosing resulted in AUC and trough concentrations similar to those observed with standard doses of indinavir /ritonavir in adults (800 mg indinavir/100 mg ritonavir twice daily), although the peak concentration was slightly decreased *[1]*. Clinical results from that trial demonstrated that virologic efficacy was good but that 4 of 21 patients developed nephrolithiasis and the overall rate of side effects and intolerance to the regimen was high *[5]*. In a study from Thailand a lower dose of indinavir (median 234 mg per meter^2) with low dose ritonavir resulted in low trough levels of indinavir in 2 of 12 children *[17]*.

In a study of 21 children receiving PI-containing antiretroviral therapy, all patients receiving indinavir experienced substantial increases in their triglyceride concentrations but no significant increases in total cholesterol occurred; blood glucose concentrations were not significantly different between baseline and follow-up evaluations *[18]*. In a study of 25 children toxicities observed with indinavir included flank pain and headache (16%), renal dysfunction (16%), hematuria (12%), and skin rash (12%) *[10]*. The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%) *[19]*. This is likely due to the difficulty in maintaining adequate hydration in children. In a study of indinavir in 54 children, 13% developed hematuria *[9]* Children treated with indinavir also have a high cumulative incidence of sterile leukocyturia, which may be accompanied by elevations in serum creatinine in the absence of clinical symptoms of nephrolithiasis *[13]*. A large analysis of more than 2,000 HIV-infected children from PACTG 219 demonstrated a hazard ratio of 1.7 for the risk of renal dysfunction among children receiving combination antiretroviral therapy with indinavir *[20]*.

References

1. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2004;48(5):1904-1907.
2. Burger DM, van Rossum AM, Hugen PW, et al. Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2001;45(3):701-705.
3. Fletcher CV, Brundage RC, Remmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother.* 2000;44(4):1029-1034.
4. Fraaij PL, Bergshoeff AS, van Rossum AM, et al. Changes in indinavir exposure over time: a case study in six HIV-1-infected children. *J Antimicrob Chemother.* 2003;52(4):727-730.
5. Fraaij PL, Verweel G, van Rossum AM, et al. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection.* 2007;35(3):186-189.
6. Gatti G, Vigano A, Sala N, et al. Indinavir pharmacokinetics and parmacodynamics in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2000;44(3):752-755.
7. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
8. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr.* 1998;132(3 Pt 1):543-546.
9. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
10. Pelton SI, Stanley K, Yogev R, et al. Switch from ritonavir to indinavir in combination therapy for HIV-1-infected children. *Clin Infect Dis.* 2005;40(8):1181-1187.
11. van Rossum AM, de Groot R, Hartwig NG, et al. Pharmacokinetics of indinavir and low-dose ritonavir in children with HIV-1 infection. *AIDS.* 2000;14(14):2209-2210.

12. van Rossum AM, Niesters HG, Geelen SP, et al. Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: a multicenter study in the Netherlands. On behalf of the Dutch Study Group for Children with HIV-1 infections. *J Pediatr.* 2000;136(6):780-788.
13. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics.* 2002;110(2 Pt 1):e19.
14. Verweel G, van Rossum AM, Hartwig NG, et al. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. *Pediatrics.* 2002;109(2):E25.
15. Vigano A, Dally L, Bricalli D, et al. Clinical and immuno-virologic characterization of the efficacy of stavudine, lamivudine, and indinavir in human immunodeficiency virus infection. *J Pediatr.* 1999;135(6):675-682.
16. Wintergerst U, Hoffmann F, Solder B, et al. Comparison of two antiretroviral triple combinations including the protease inhibitor indinavir in children infected with human immunodeficiency virus. *Pediatr Infect Dis J.* 1998;17(6):495-499.
17. Plipat N, Cressey TR, Vanprapar N, et al. Efficacy and plasma concentrations of indinavir when boosted with ritonavir in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J.* 2007;26(1):86-88.
18. Temple ME, Koranyi KI, Nahata MC. Lipodystrophy in HIV-infected pediatric patients receiving protease inhibitors. *Ann Pharmacother.* 2003;37(9):1214-1218.
19. Food and Drug Administration (FDA). Indinavir product label. 2006; http://www.fda.gov/medwatch/safety/2006/Dec_PIs/Crixivan_PI.pdf.
20. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J.* 2009;28(7):619-625.

Lopinavir/Ritonavir (LPV/r, Kaletra)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 80 mg/20 mg LPV/r/mL (contains 42.4% alcohol by volume)
Pediatric tablets: 100 mg/25 mg LPV/r
Tablets: 200 mg/50 mg LPV/r

Dosing Recommendations

Neonate/Infant dose:
Infants <14 days: No data on appropriate dose or safety. Should not be used in preterm infants in the immediate postnatal period.

Infants 14 days to 6 months: Once-daily dosing is **not** recommended.

The recommended dose of the oral solution is 300 mg/75 mg LPV/r per m^2 of body surface area or 16 mg/4 mg LPV/r per kg of body weight twice daily. Do not administer LPV/r with efavirenz (EFV), nevirapine (NVP), fosamprenavir (FPV), or nelfinavir (NFV) in infants <6 months of age.

Use of 300 mg/75 mg LPV/r per m2 of body surface area in infants <6 months of age is associated with lower LPV trough levels than those found in adults; infants should be evaluated and LPV dosing adjusted for growth at frequent intervals (see discussion).

Pediatric dose (>6 months to 18 years):
*For individuals **not** receiving concomitant EFV, NVP, FPV, or NFV:*

Once-daily dosing is **not** recommended.

Body surface area dosing:
230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily

Weight-based dosing:
<15 kg: 12 mg/3 mg LPV/r/kg body weight per dose twice daily

≥15 kg to 40 kg: 10 mg/2.5 mg LPV/r/kg body weight per dose twice daily

≥40 kg: 400 mg/100 mg LPV/r per dose twice daily

Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents **Without** Concomitant EFV, NVP, FPV, or NFV.

Body Weight (kg)	Body Surface Area (m^2)*	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 25 kg	≥0.6 to <0.9 m^2	2
>25 to 35 kg	≥0.9 to <1.4 m^2	3
>35 kg	≥1.4 m^2	4 (or two 200 mg/50 mg LPV/r adult tablets)

*Oral solution is available for children age 6 months to 18 years with a

Selected Adverse Events

- GI intolerance, nausea, vomiting, diarrhea
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistibution
- Possible increased bleeding in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsade de pointes

Special Instructions

- LPV/r tablets can be administered without regard to food, but recognize that administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food. A high fat meal increases absorption, especially of the liquid preparation, which may enhance effectiveness by increasing drug exposure.
- If coadministered with didanosine (ddI), ddI should be given 1 hour before or 2 hours after LPV/r.
- LPV/r oral solution can be kept at room temperature up to 77ºF (25ºC) if used within 2 months. If kept refrigerated (2º to 8ºC or 36º to 46ºF) LPV/r oral solution remains stable until the expiration date printed on the label.
- LPV resistance-associated substitutions: LPV/r can be administered once daily (800 mg/200 mg) in adults with fewer than 3 LPV resistance-associated substitutions. Once-daily administration of LPV/r is not recommended for adult patients with 3 or more of the following LPV resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- CYP 3A4 inhibitor and substrate.
- Dosing of LPV/r in patients with hepatic impairment: LPV/r is primarily metabolized by the liver. Caution should be used when administering LPV to patients with hepatic impairment. No dosing information is

body surface area <0.6 m^2 or those who are unable to reliably swallow a tablet; dosing should be calculated based on body surface area or weight as above.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

Pediatric dose (>6 months to 18 years):
For individuals receiving concomitant NVP, EFV, FPV, or NFV. (These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs and/or in treatment-experienced patients in whom reduced susceptibility to LPV is suspected [such as those with prior treatment with other PIs].)

Once-daily dosing is **not** recommended.

Body surface area dosing:
300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily

Weight-based dosing:
<15 kg: 13 mg /3.25 mg LPV/r per kg body weight per dose twice daily

≥15 kg to 45 kg: 11 mg/2.75 mg LPV/r per kg body weight per dose twice daily

≥45 kg: Use adult dose twice daily.

Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children **With** Concomitant EFV, NVP, FPV , or NFV		
Body Weight (kg)	Body Surface Area (meter^2)*	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 20 kg	≥0.6 to <0.8 m^2	2
>20 to 30 kg	≥0.8 to <1.2 m^2	3
>30 to 45 kg	≥1.2 to <1.7 m^2	4 (or two 200 mg/50 mg LPV/r tablets)
>45 kg	≥1.7 m^2	4 or 6 (or two or three 200 mg/50 mg LPV/r adult tablets)**

*Oral solution is available for children age 6 months to 18 years with a body surface area <0.6 m^2 or those who are unable to reliably swallow a tablet; dosing should be calculated based on body surface area or weight as above.
**The higher dose may be considered in treatment-experienced patients where decreased sensitivity to LPV is suspected due to clinical history or documented by resistance testing.

Use of 230 mg/57.5 mg LPV/r per m2 of body surface area (when not coadministered with NVP, EFV, FPV, or NFV) or use of 300 mg/75 mg LPV/r per m2 of body surface area in children (when coadministered with NVP, EFV, FPV, or NFV) is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults. Therefore, some clinicians may choose to initiate therapy with higher doses of LPV/r when coadministered with these drugs or in PI-experienced pediatric patients who may have reduced PI currently available for children or adults with hepatic insufficiency.

- In the coformulation of LPV/r, the RTV acts as a pharmacokinetic enhancer, not as an antiretroviral agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

susceptibility (see discussion). **Adult (>18 years) dose**: *In patients with fewer than 3* LPV*-associated mutations (see Special Instructions for list):* 800 mg/200 mg LPV/r once daily; **or** 400 mg/100 mg LPV/r twice daily. Do **not** use once-daily dosing in children or adolescents. Once-daily dosing should not be used in patients receiving concomitant therapy with EFV, NVP, FPV, or NFV. *In patients with 3 or more LPV-associated mutations(see Special Instructions for list):* 400 mg/100 mg LPV/r twice daily *In patients receiving concomitant NVP, EFV, FPV, or NFV):* FDA-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of 2 tablets of 200/50 mg LPV/r and 1 tablet of 100 mg/25 mg LPV/r. Most Panel members would use 600 mg/150 mg LPV/r for ease of dosing. Once-daily dosing should **not** be used. *LPV/r in combination with saquinavir (SQV) hard gel capsules (Invirase) or in combination with maraviroc (MVC):* SQV and MVC doses may need modification. See sections on **SQV** or **MVC**.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Fluticasone, a commonly used inhaled steroid, should not be used in patients treated with lopinavir/ritonavir.

Major Toxicities:

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving lopinavir/ritonavir with other antiretroviral drugs; hyperlipidemia, especially hypertriglyceridemia.
- *Less common (more severe):* Lipodystrophy.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life threatening in rare cases). Possible increased bleeding episodes in patients with hemophilia. PR interval prolongation. QT interval prolongation and torsade de pointes may occur. Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants because life-threatening bradyarrhthymias and cardiac dysfunction have been described with its use in such infants *[1-2]*.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/LPV.html**).

Pediatric Experience:

Lopinavir/ritonavir has been studied in HIV-infected children in combination with NRTIs and NNRTIs *[3-16]*. Ritonavir acts as a pharmacokinetic enhancer by inhibiting the metabolism of lopinavir and therefore increasing the plasma concentration of lopinavir.

Abbott Laboratories Study M98-940 was a Phase I/II open label study that evaluated the pharmacokinetics, tolerability, safety, and efficacy of lopinavir/ritonavir oral solution and either 2 NRTIs or nevirapine plus up to 2 NRTIs in 100 pediatric patients. Through 48 weeks of therapy, the proportion of patients with HIV RNA <400 copies/mL was 37 of 44 (84%) for antiretroviral-

naïve patients and 42 of 56 (75%) for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral-naïve and 284 cells/mm^3 for antiretroviral-experienced patients. In patients with HIV RNA >400 copies/mL at 24 or 48 weeks, there were no detectable changes in susceptibility to lopinavir compared with baseline isolates, although there were resistance mutations to NRTIs and NNRTIs in the rebound isolates *[17]*.

There is some controversy about the dosing of lopinavir/ritonavir in children. Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The "directly scaled" dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m^2. For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per $meter^2$. However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C_{trough} to that observed in adults, the pediatric dose needs to be increased 30% over the directly body surface area-scaled dose.

For 12 children age 6 months to 12 years receiving 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 4.74 ± 2.93 mcg/mL (about 67% of the adult value of 7.1 ± 2.9 mcg/mL) *[4]*. For 15 children age 6 months to 12 years treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 7.91 ± 4.52 mcg/mL, similar to that in adults treated with 400 mg/100 mg lopinavir/ritonavir twice daily *[4]*. Therefore, some clinicians may choose to initiate therapy in children age 6 months to 12 years using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug-label recommended 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily *[12]*.

The pharmacokinetics of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily was evaluated in infants younger than 6 weeks of age *[18]* and infants 6 weeks to 6 months of age *[14]*. Pharmacokinetic values found in these studies are compared to those in older children *[4]* and adults *[17]* in the table below. Values are means; all data shown performed in the absence of NNRTIs.

	Adults *[17]*	**Children** *[4]*	**Children** *[4]*	**Infants 6 wk–6 mo** *[14]*	**Infants <6 weeks** *[18]*
N	19	12	15	18	9
Dose LPV	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC mcg*hr/ml	92.6	72.6	116	74.5	43.4
C_{max} mcg/ml	9.8	8.2	12.5	9.4	5.2
C_{trough} mcg/ml	7.1	4.7	7.9	2.7	2.5
C_{min} mcg/ml	5.5	3.4	6.5	2.0	1.4

Even at this higher dose, predose (C_{trough}) levels were lower in infants than in children >6 months of age and were lower in the youngest infants at age <6 weeks compared with those between 6 weeks and 6 months. Predose (C_{trough}) levels were highly variable, and lower values (median 1.37 mcg/mL; range 0.13–5.98) were found in infants without viral suppression at 16 weeks compared with the higher predose (C_{trough}) values (median 2.28 mcg/mL; range 0.49–8.01) found in those infants with virologic suppression at 16 weeks (N = 17; p = 0.37) *[14]*. Because infants gain weight rapidly in the first months of life, one important way to optimize lopinavir dosing is to weigh the patient and adjust the dose for growth at frequent intervals. Some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m^2 body surface area dose to let the infant "grow into" the 300 mg/m^2 body surface area amount.

For children, as in adults, the lopinavir C_{trough} is further reduced by concurrent treatment with NNRTIs or concomitant fosamprenavir or nelfinavir and, as in adults, higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL *[4]*. For 12 children treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily, the mean C_{trough} was 5.62 ± 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than adults *[4, 12]*. In a study of 15 children with HIV infection treated with the combination of lopinavir/ritonavir using an increased dose of 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, the median 12-hour lopinavir trough was 5.7 mcg/mL, but there was 34-fold interindividual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV *[5]*. A pharmacokinetic study in 20 children 10 to 16 years of age treated with the combination of lopinavir/ritonavir 300 mg/75

mg per m^2 of body surface area twice daily plus efavirenz 350 mg/m^2 of body surface area once daily showed adequacy of the lopinavir trough values *[19]*.

Lopinavir/ritonavir 800 mg/200 mg once daily is FDA approved for treatment of HIV infection in therapy-naïve adults >18 years of age. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring because of high interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21/59 (35.6%) of patients *[20-23]*.
Lopinavir/ritonavir has been shown to be effective as salvage therapy in children with HIV and severe immune suppression *[7, 24]*, although patients with greater prior exposure to antiretrovirals may have slower reductions in virus load to undetectable concentrations *[10, 24]* and less robust response in CD4 percentage *[25]*. Twice-daily doses of lopinavir used in this cohort were 230–300 mg/m^2 of body surface area in 39% of patients, 300–400 mg/m^2 of body surface area in 35%, and >400 mg/m^2 of body surface area per dose in 4% *[25]*.

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just prior to a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC_{50}). The ratio of C_{trough} to EC_{50} is called the inhibitory quotient, and in both adults and children treated with lopinavir/ritonavir, virus load reduction is more closely associated with inhibitory quotient than with either the C_{trough} or EC_{50} alone *[3, 26-28]*. A study of the practical application of the inhibitory quotient to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (with nevirapine or efavirenz) *[16]*. A modeling study suggests the potential utility of therapeutic drug monitoring in children previously treated with protease inhibitors and now on salvage therapy with lopinavir/ritonavir *[29]*.

References

1. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
2. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.
3. Havens P, Frank M, Cuene B, et al. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m2/dose in children and adolescents with HIV infection. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 937.
4. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2003;22(3):216-224.
5. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr.* 2005;39(1):63-68.
6. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
7. Resino S, Bellon JM, Ramos JT, et al. Salvage lopinavir-ritonavir therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(10):923-930.
8. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J.* 2005;24(10):867-873.
9. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS.* 2004;18(2):247-255.
10. Resino S, Galan I, Perez A, et al. Immunological changes after highly active antiretroviral therapy with lopinavir-ritonavir in heavily pretreated HIV-infected children. *AIDS Res Hum Retroviruses.* 2005;21(5):398-406.
11. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
12. Verweel G, Burger DM, Sheehan NL, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir Ther.* 2007;12(4):453-458.
13. Jullien V, Urien S, Hirt D, et al. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother.* 2006;50(11):3548-3555.
14. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.

15. Pinto J, Robbins B, Chen J, et al. Pharmacokinetics and 24-week efficacy and safety of lopinavir/ritonavir in HIV-1 infected infants <6 weeks of age. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections (CROI); Feb 25-28, 2007; Los Angeles, CA. Abstract 716.
16. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
17. Food and Drug Administration (FDA). Lopinavir-ritonavir (Kaletra) product label. 2010; http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021226s030lbl.pdf.
18. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
19. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2009;28(2):159-161.
20. Rosso R, Di Biagio A, Dentone C, et al. Lopinavir/ritonavir exposure in treatment-naive HIV-infected children following twice or once daily administration. *J Antimicrob Chemother.* 2006;57(6):1168-1171.
21. van der Lee M, Verweel G, de Groot R, et al. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2006;11(4):439-445.
22. la Porte C, van Heeswijk R, Mitchell CD, et al. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther.* 2009;14(4):603-606.
23. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther.* 2008;13(8):1087-1090.
24. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
25. Larru B, Resino S, Bellon JM, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. *J Antimicrob Chemother.* 2008;61(1):183-190.
26. Casado JL, Moreno A, Sabido R, et al. Individualizing salvage regimens: the inhibitory quotient (Ctrough/IC50) as predictor of virological response. *AIDS.* 2003;17(2):262-264.
27. Delaugerre C, Teglas JP, Treluyer JM, et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. *J Acquir Immune Defic Syndr.* 2004;37(2):1269-1275.
28. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 2003;47(1):350-359.
29. Rakhmanina N, van den Anker J, Baghdassarian A, et al. Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2009;53(6):2532-2538.

Nelfinavir (NFV, Viracept)

For additional information see: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Powder for oral suspension: 50 mg/1 level gram scoopful (200 mg/1 level teaspoon)
(Oral powder contains 11.2 mg phenylalanine per gram of powder.)
Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonatal/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose (2–13 years):
45–55 mg/kg twice daily **or** 25–35 mg/kg three times daily

Adolescent/Adult dose:
1,250 mg (five 250-mg tablets or two 625-mg tablets) twice daily **or** 750 mg (three 250-mg tablets) three times daily

(Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.)

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- Serum transaminase elevations

Special Instructions

- Administer with meal or light snack.
- If coadministered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- Powder for oral suspension may be mixed with water, milk, pudding, ice cream, or formula; mixture is stable for up to 6 hours.
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Patients unable to swallow the tablets can dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding.

Metabolism

- CYP2C19 and 3A4 substrate.
- Metabolized to active M8 metabolite.
- CYP3A inhibitor.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Nelfinavir is metabolized in part by CYP3A4 and is a substrate for CYP2C19 and 3A4. However, ritonavir boosting does not significantly increase nelfinavir concentrations and coadministration is not recommended.
- There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea (most common). Asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/NFV.html**).

Pediatric Experience: Nelfinavir has been extensively studied in HIV-infected children in combination with other antiretroviral drugs *[1-23]*. In children 2–13 years of age receiving nelfinavir as part of triple antiretroviral therapy in randomized trials, the

proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. Virologic and immunologic response to nelfinavir-based therapy has varied by prior antiretroviral treatment, the number of drugs included in the combination regimen, patient age, and dose used in the study.

Highly variable drug exposure remains a significant problem with the use of nelfinavir in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared with adults and difficulties with adherence to adequate food intake with dosing. In earlier studies, lower doses were used (20–30 mg/kg body weight per dose three times daily) than are currently recommended (45–55 mg/kg body weight per dose twice daily), accounting for some of the lower response rates. The relatively poor ability of nelfinavir to control plasma viremia in infants and children may be related in part to its reduced potency compared with other PIs or NNRTIs, as shown by studies in adults and adolescents *[23-24]*.

Poor outcome with nelfinavir in children may be related in part to lack of palatability of the powder formulation and pharmacokinetic differences in infants, children, and adolescents compared with adults *[6]*. The consistency of food or formula is altered by the addition of pediatric nelfinavir powder, making the drug/admixture unpalatable to some children. These children may prefer the bitterness of the crushed tablets to the sandy consistency of food or formula containing nelfinavir powder. In the PENTA-7 trial, 7 of 20 (35%) infants who started therapy with the nelfinavir powder were switched to crushed tablets because of the difficulty of administering the powder to infants *[1]*.

Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir pharmacokinetics and the virologic responses to combination therapy in HIV-1-infected children. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir pharmacokinetics and virologic response in HIV-1-infected children *[25]*.

Better control of plasma viremia has been observed in antiretroviral-naïve than antiretroviral-experienced children receiving nelfinavir *[8, 11, 16]*. In treatment-experienced patients, better response rates have been seen with 4-drug regimens that have included 2 NRTIs plus an NNRTI *[11, 21]*. When lopinavir/ritonavir was compared with nelfinavir for salvage therapy in 35 treatment-experienced patients after 18 months, 50% of children receiving lopinavir/ritonavir had HIV RNA concentrations <400 copies/mL, compared with <20% of children receiving nelfinavir *[18]*.

Antiviral response in children <2 years of age is significantly less than in older children *[16, 19, 26]*. Improved virologic responses may be seen with nelfinavir-based therapy when it is used as part of a four-drug regimen in children <2 years of age *[14]*. Infants have even lower drug exposures and higher variability in plasma concentrations than children <25 kg; the presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors *[3, 15]*. Even with doses of 150 mg/kg/day (given 2–3 times daily), 16.7% of children had peak concentrations and 27.8% of children had 24-hour AUC that were below the 10th percentile of adult values *[13]*. Although it is suggested that dosing in infants might improve if a mg/m^2 of body surface area dosing regimen were used *[2-3]*, such dosing is not recommended at this time. A population pharmacokinetic study predicts three-times daily dosing may be superior to twice-daily dosing in infants <2 months of age *[27]*. This model requires confirmation in infants.

Determining an appropriate and effective dose of nelfinavir in children is complicated by highly variable drug pharmacokinetics. In children 2–12 years of age, administration of a nelfinavir 30 mg/kg/dose three times daily achieves lower drug exposure than administration of a 55 mg/kg/dose twice daily, and this difference is most marked in children weighing <25 kg *[20]*. Children <25 kg may have less than half the drug exposure than children >25 kg when comparable body weight-adjusted doses are used *[7]*. The variability of drug exposure at any given dose is much higher for children than adults *[9]*, which has been attributed at least in part to differences in the diet between children and adults. Two population pharmacokinetic studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children *[27-28]*.

Studies in adults and children have demonstrated an increased risk of virologic failure associated with low nelfinavir drug exposure, particularly with a nelfinavir C_{min} <1.0 mcg/mL *[29-31]*. In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of those with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough <0.8 mcg/mL *[32]*. It is of note that the median age of the group with C_{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} >0.8 mcg/mL was 8.3 years *[32]*. Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir *[29, 33]*. Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of therapeutic drug monitoring and appropriate dose adjustment might be even greater for children. A response rate of 78% was found in a recent pediatric study in which concentrations of nelfinavir and M8 were reported to treating physicians, suggesting a benefit of pharmacokinetic

monitoring in children *[28]*. In PACTG 382, among 50 children 3–16 years of age receiving both efavirenz and nelfinavir, better virologic outcomes (HIV RNA <400 copies/mL) occurred in those patients when nelfinavir AUC_{8h} was greater than the first quartile (>10 mg*h/L) when compared with those below the first quartile: 89% versus 42%, respectively *[5]*. Better virologic responses were obtained when doses were adjusted to achieve target AUC values, an approach that requires therapeutic drug monitoring.

References

1. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
2. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of nelfinavir in children: influencing factors and dose implications. *Antivir Ther.* 2003;8(3):215-222.
3. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J.* 2001;20(8):746-751.
4. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
5. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306.
6. Fletcher CV. Antiretroviral therapy for HIV-infected infants: progress and pitfalls. *AIDS.* 2004;18(2):325-326.
7. Floren LC, Wiznia A, Hayashi S, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics.* 2003;112(3 Pt 1):e220-227.
8. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS.* 1999;13(13):1653-1658.
9. Gatti G, Castelli-Gattinara G, Cruciani M, et al. Pharmacokinetics and pharmacodynamics of nelfinavir administered twice or thrice daily to human immunodeficiency virus type 1-infected children. *Clin Infect Dis.* 2003;36(11):1476-1482.
10. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
11. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
12. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis.* 1999;28(5):1109-1118.
13. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 2003;22(1):48-55.
14. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
15. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
16. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
17. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis.* 2006;6:107.
18. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
19. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
20. Schuster T, Linde R, Wintergerst U, et al. Nelfinavir pharmacokinetics in HIV-infected children: a comparison of twice daily and three times daily dosing. *AIDS.* 2000;14(10):1466-1468.
21. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
22. van Heeswijk RP, Scherpbier HJ, de Koning LA, et al. The pharmacokinetics of nelfinavir in HIV-1-infected children. *Ther Drug Monit.* 2002;24(4):487-491.
23. Wu H, Lathey J, Ruan P, et al. Relationship of plasma HIV-1 RNA dynamics to baseline factors and virological responses to highly active antiretroviral therapy in adolescents (aged 12-22 years) infected through high-risk behavior. *J Infect Dis.* 2004;189(4):593-601.

24. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
25. Saitoh A, Capparelli E, Aweeka F, et al. CYP2C19 genetic variants affect nelfinavir pharmacokinetics and virologic response in HIV-1-infected children receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2010;54(3):285-289.
26. Food and Drug Administration (FDA). Nelfinavir (Viracept®) product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021503s006lbl.pdf.
27. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother.* 2006;50(3):910-916.
28. Crommentuyn KM, Scherpbier HJ, Kuijpers TW, et al. Population pharmacokinetics and pharmacodynamics of nelfinavir and its active metabolite M8 in HIV-1-infected children. *Pediatr Infect Dis J.* 2006;25(6):538-543.
29. Burger DM, Hugen PW, Aarnoutse RE, et al. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. *Ther Drug Monit.* 2003;25(1):73-80.
30. Gonzalez de Requena D, Nunez M, de Mendoza C, et al. Nelfinavir plasma concentrations in patients experiencing early failure with nelfinavir-containing triple combinations. *AIDS.* 2003;17(3):442-444.
31. Pellegrin I, Breilh D, Montestruc F, et al. Virologic response to nelfinavir-based regimens: pharmacokinetics and drug resistance mutations (VIRAPHAR study). *AIDS.* 2002;16(10):1331-1340.
32. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr.* 2004;145(3):403-405.
33. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS.* 2003;17(8):1157-1165.

Ritonavir (RTV, Norvir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Oral solution (contains 43% alcohol by volume): 80 mg/mL
Capsules: 100 mg
Tablets: 100 mg

Dosing Recommendations

RTV as a pharmacokinetic enhancer:
The major use of RTV is as a pharmacokinetic enhancer of other PIs. The dose of RTV recommended varies with the different PIs. See dosing information for specific PIs.

In the unusual situation when RTV is prescribed as sole PI:
See manufacturer guidelines.

Selected Adverse Events

- GI intolerance, nausea, vomiting, diarrhea
- Paresthesias—circumoral and extremities
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer with food to increase absorption and help decrease gastrointestinal side effects.
- If RTV is prescribed with didanosine (ddI), administer drugs 2 hours apart.
- Refrigerate capsules only if the capsules will not be used within 30 days or cannot be stored below 77° F (25° C). Tablets are heat stable.
- Store oral solution at room temperature 68–77°F (20–25°C). Do not refrigerate. Shake well before use.
- Oral solution has limited shelf life; use within 6 months.

To increase tolerance of oral solution in children, try the following:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
- Before administration, give the child ice chips, popsicles, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds or peanut butter to coat the mouth.
- After administration, give the child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- CYP3A4 and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- Dosing of RTV in patients with hepatic impairment: RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data for dosing adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions and overlapping toxicities.
- Avoid concomitant use of intranasal/inhaled fluticasone.

Resistance: When ritonavir is used as a pharmacokinetic enhancer, resistance to ritonavir is not clinically relevant.

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias, lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.

Pediatric Experience: Ritonavir is typically used as a pharmacokinetic enhancer of other PIs in children. Ritonavir acts by inhibiting the metabolism of the other PI, therefore increasing the plasma concentration of the second PI. Lopinavir/ritonavir, a PI coformulation, has been well studied in children and is the preferred PI for initial therapy in children (see **Lopinavir/Ritonavir**). Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, and atazanavir are now available (see individual PIs for more specific information).

Although ritonavir has been well studied, its use in children as a sole PI for initial therapy is recommended only under certain rare circumstances. Ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. Additionally, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than 2 years of age, and doses of 350–450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group *[1-12]*.

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily *[13]*. There have been reports of potentially life threatening arrhythmias in premature newborn infants treated with lopinavir/ritonavir and thus it should not be used in this group of patients *[14-15]*. The impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) is not known, and coadministration should be undertaken with caution. In addition, patients with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy may be at increased risk of developing cardiac conduction abnormalities, and ritonavir should be used with caution in these patients.

References

1. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2004;48(5):1904-1907.
2. Fletcher CV, Yogev R, Nachman SA, et al. Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with human immunodeficiency virus infection. *Pharmacotherapy.* 2004;24(4):453-459.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
5. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
6. Mueller BU, Nelson RPJr, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.

7. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
8. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
9. Thuret I, Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. *AIDS.* 1999;13(1):81-87.
10. van Rossum AM, de Groot R, Hartwig NG, et al. Pharmacokinetics of indinavir and low-dose ritonavir in children with HIV-1 infection. *AIDS.* 2000;14(14):2209-2210.
11. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.
12. Yogev R, Lee S, Wiznia A, et al. for the Pediatric AIDS Clinical Trials Group 338 Study Team. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(2):119-125.
13. Changes to Norvir labeling. *AIDS Patient Care STDS.* 2008;22(10):834-835.
14. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
15. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.

Saquinavir (SQV, Invirase)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Hard gel capsules (HGC): 200 mg
Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children.

Investigational doses in treatment-experienced children:
SQV must be boosted with ritonavir (RTV):

<2 years of age:
Not recommended—no dose has been determined.

≥2 years of age (conditional recommendation based on limited data):

Weight (kg)	Dose SQV + RTV
5– <15 kg	SQV 50mg/kg + RTV 3 mg/kg, both twice daily
15–40 kg	SQV 50mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50mg/kg + RTV 100 mg, both twice daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

SQV in combination with lopinavir/ritonavir (LPV/r)
Pediatric (≥7 years) dose:
SQV 750 mg/m^2 (max 1,600 mg) + LPV/r 400/100 mg/m^2, both twice daily

or

SQV 50 mg/kg + LPV/r 230/57.5 mg/m^2, both twice daily

There are limited or no data on SQV + LPV/r dosing for children <7 years of age. See pediatric experience section for details.

Adolescent (≥16 years)/Adult dose:
SQV 1,000 mg + RTV 100 mg, both twice daily
Should be taken within 2 hours after a full meal. SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

Selected Adverse Events

- GI intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer within 2 hours after a full meal to increase absorption.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.

Metabolism

- Cytochrome P450 CYP3A4 substrate, 90% metabolized in the liver.
- Use with caution in patients with hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Saquinavir is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there is potential for numerous drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and torsades de pointes.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/SQV.html**).

Pediatric Experience: Saquinavir has been studied with NRTIs and other PIs in HIV-infected children *[1-6]*. Initial studies suggested that saquinavir could not be used without boosting by ritonavir or lopinavir/ritonavir. A pharmacokinetic analysis of 5 children younger than 2 years of age and 13 children between the ages of 2 and 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir revealed that drug exposure was lower in children <2 years whereas drug exposure was adequate in those 2 to 5 years of age *[7]*. For this reason, saquinavir should not be given to children younger than 2 years old until an appropriate dose is identified. In children ≥2 years of age, a dose of 50mg/kg twice daily (maximum dose = 1,000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 to 40 kg) resulted in AUC and C_{trough} values similar to those in older children *[8-9]* and adults. Because there is no pediatric formulation, in one study saquinavir was formulated by breaking open the 200-mg hard gel capsules and mixing capsule contents with sugar syrup, jam, or baby formula. Sorbitol syrup was used for patients with diabetes or glucose intolerance *[7]*.

Both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens are promising in the salvage therapy setting *[1, 3-6, 8-10]*. In a study evaluating the addition of saquinavir (750 mg/m^2 of body surface area every 12 hours, maximum dose 1,600 mg) to a regimen containing lopinavir/ritonavir dosed at 400/100 mg/m^2 twice daily (for patients not concurrently taking an NNRTI) or lopinavir/ritonavir 480/120 mg/m^2 twice daily for patients concurrently administered an NNRTI, 18 subjects (median age 14.2 years, range 7.7–17.6) were enrolled. The addition of saquinavir at these doses was well tolerated and did not appear to alter lopinavir pharmacokinetics. Saquinavir dosing was adjusted in 4 subjects (decreased in 3, increased in 1) *[10]*.

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance. In this group, saquinavir was dosed at 50 mg/m^2 and lopinavir/ritonavir was dosed at 230/57.5 mg/m^2, all twice daily. After 96 weeks of treatment, 74% of the children achieved an undetectable plasma RNA load at <50 copies/ml. Therapeutic drug monitoring was used to establish adequate C_{min} values and to aid with alterations in drug dosage based upon toxicity. Most C_{min} values for saquinavir were above the desired trough value of 0.1 mg/l. The average C_{min} throughout 96 weeks for saquinavir was 1.37 mg/l, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8mg/kg). Median total cholesterol and HDL values increased significantly through 96 weeks from 144 to 196 mg/dl and from 44 to 57 mg/dl, respectively *[8-9]*.

References

1. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
2. De Luca M, Miccinesi G, Chiappini E, et al. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol.* 2005;18(4):729-735.
3. Grub S, DeLora P, Ludin E, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther.* 2002;71(3):122-130.
4. Hoffmann F, Notheis G, Wintergerst U, et al. Comparison of ritonavir plus saquinavir- and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. *Pediatr Infect Dis J.* 2000;19(1):47-51.
5. Kline MW, Brundage RC, Fletcher CV, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2001;20(7):666-671.
6. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
7. Haznedar J, Zhang A, Labriola-Tompkins E, et al. A pharmacokinetic study of ritonavir-boosted saquinavir in HIV-infected children 4 months to <6 years old. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA.

8. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
9. Bunupuradah T, van der Lugt J, Kosalaraksa P, et al. Safety and efficacy of a double-boosted protease inhibitor combination, saquinavir and lopinavir/ritonavir, in pretreated children at 96 weeks. *Antivir Ther.* 2009;14(2):241-248.
10. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.

Tipranavir (TPV, Aptivus)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral solution: 100 mg TPV/ml with 116 IU vitamin E/ml
Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose is higher than that used for other PIs.

Pediatric dose (<2 years):
Not approved for use in children <2 years of age.

Pediatric dose (2–18 years):
Body surface area dosing:
TPV 375 mg/m2 + RTV 150 mg/m2, both twice daily
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily

Weight-based dosing:
TPV 14 mg/kg + RTV 6 mg/kg, both twice daily
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily

Adult dose:
TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily

Selected Adverse Events

- Intracranial hemorrhage (rare)
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- TPV can be taken with or without food; however, it is recommended that RTV be taken with food. Therefore, the combination may be better tolerated if taken with a meal or snack.
- The oral solution contains 116 IU of vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should not take any supplemental vitamin E greater than a standard multivitamin.
- TPV contains a sulfonamide component. The potential for cross sensitivity between TPV and other drugs in the sulfonamide class is unknown. TPV should be used with caution in patients with sulfonamide allergy.
- Store oral solution at room temperature (77^{o} F); do not refrigerate or freeze. Oral solution must be used within 60 days after first opening bottle.
- Capsules can be kept at room temperature (up to 77^{o}F or 25^{o}C) if used within 2 months. Refrigerate capsules if longer storage or warmer room temperatures anticipated.
- Use TPV with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Metabolism

- Cytochrome P450 CYP3A4 substrate.
- Renal impairment: No adjustment required.
- Liver impairment: No adjustment required for mild impairment; use contraindicated for moderate-to-severe impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities:

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Laboratory abnormalities are elevated transaminases, cholesterol, and triglycerides.
- *Less common (more severe):* Lipodystrophy. Clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Possible association with increased risk of intracranial hemorrhage.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/TPV.html**).

Pediatric Experience: Tipranavir is approved in children ≥2 years of age; approval was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics of tipranavir/ritonavir in HIV-infected children (PACTG 1051/BI-1182.14). This study enrolled treatment-experienced children (with the exception of 3 treatment-naïve patients) 2–18 years of age (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children were randomized to 1 of 2 doses of tipranavir coadministered with ritonavir in 3 age strata: tipranavir/ritonavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg per m^2 body surface area (high dose, 57 patients) twice daily plus optimized background therapy. All children initially received the oral solution; patients who were ≥12 years of age and received the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily could change to tipranavir capsules. At baseline, greater than 50% of patients were resistant to all commercially available protease inhibitors, and the number of protease resistance mutations increased with age *[1]*. Among the low-dose group (tipranavir/ritonavir 290/115 mg/m^2 body surface area), 40% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL at 48 weeks. Among those receiving the higher dose (tipranavir/ritonavir 375/150 mg/m^2 body surface area), 46% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL at 48 weeks. The proportion of patients with HIV RNA <400 copies/mL tended to be greater in the youngest group of patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 cell count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, side effects were similar between treatment groups. Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs due to adverse events. The most common adverse events were gastrointestinal disturbances. Moderate or severe laboratory toxicity was seen in 11% of children (primarily increase in GGT and CPK). Four patients (all in the low-dose group and three-fourths in the younger age group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus the high-dose group reached statistical significance ($p = 0.04$). In a multivariate model, 3 variables predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100K copies/mL, in that order. GIQ is a ratio of the median tipranavir trough concentration divided by the number of tipranavir mutations. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, the high-dose regimen has been recommended.

Pharmacokinetics of the liquid formulation at steady state were assessed *[2]*. For children 2 to <12 years of age, tipranavir trough concentrations for pediatric patients receiving tipranavir/ritonavir 290/115 mg/m^2 body surface area were consistent with tipranavir trough concentrations achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children 12 to 18 years of age required a higher dose (375/150 mg/m^2 body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard tipranavir/ritonavir dose. Population pharmacokinetic analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age *[2]*. Based on these studies the final dose of tipranavir/ritonavir was chosen as 375/150 mg/m^2 body surface area twice daily.

Vitamin E is an excipient in the oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir per ml of solution. Use of the recommended dose of tipranavir (14 mg per kg body weight) results in a vitamin E dose of 16 IU per kg

body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. The resultant high dose of vitamin E may lead to an increase in bleeding episodes, which were seen in 5.75% of children receiving the oral solution and 14.3% of children receiving capsules *[1]*.

References

1. Salazar JC, Cahn P, Yogev R, et al. Efficacy, safety and tolerability of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents. *AIDS.* 2008;22(14):1789-1798.
2. Sabo J, Cahn P, Della Negra M, et al. Population pharmacokinetic (PK) assessment of systemic steady-state tipranavir (TPV) concentrations for HIV+ pediatric patients administered tipranavir/ritonavir (TPV/r) 290/115 mg/m2 and 375/150 mg/m2 BID (BI 1192.14 and PACTG 1051 study team). Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI); February 5-9, 2006; Denver, CO. Abstract R136, poster 687.

ENTRY AND FUSION INHIBITORS

Enfuvirtide (ENF, T-20, Fuzeon)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Lyophilized powder for injection:
108-mg vial of ENF. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience kit*:*
60 single-use vials of ENF (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes

Dosage Recommendations

Pediatric/Adolescent dose (6–16 years):
Children <6 years:
Not approved for use in children <6 years of age.

Children ≥6 years:
2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen

Adolescent (>16 years)/Adult dose:
90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen

Selected Adverse Events

- Local injection site reactions
- Increased bacterial pneumonia (unclear association)
- Hypersensitivity reaction—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous injections. ENF injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject ENF immediately or keep refrigerated in the original vial until use. Reconstituted ENF must be used within 24 hours.
- Must be given subcutaneously; severity of reactions increased if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions apply ice or heat after injection or gently massage injection site to better disperse the dose. There are reports of injection-associated neuralgia and parasthesia if alternative delivery systems, such as needle-free injection devices, are used.
- Advise patient/caregiver of the possibility of a hypersensitivity reaction; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a hypersensitivity reaction.

Metabolism

- Catabolism to constituent amino acids.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents****.)***:

- There are no known significant drug interactions.

Major Toxicities:

- *More common:* Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association) and local site cellulitis (up to 11% in certain subgroups of patients in pediatric studies) *[1]*.
- *Rare:* Hypersensitivity reactions (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate

medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ENF.html**).

Pediatric Experience: Enfuvirtide has been studied in HIV-infected children in combination with other antiretroviral drugs *[1-5]*. PACTG 1005 initially studied enfuvirtide in 14 HIV-infected children age 4–12 years with incomplete viral suppression (plasma RNA >10,000 copies/ml) while on a stable antiretroviral regimen consisting of 2 NRTIs plus an NNRTI or a PI for ≥16 weeks *[2]*. Part A included a single-dose pharmacokinetic evaluation of enfuvirtide given subcutaneously at 15, 30, or 60 mg/m^2 of body surface area. The dose of enfuvirtide that reliably resulted in the target trough concentration (1,000 ng/mL) was 60 mg/m^2 of body surface area per dose, the approximate "equivalent" of a 90-mg dose delivered subcutaneously to an adult with a body surface area of 1.7 m^2. This led to the recommended pediatric label dose in children age 6–16 years of 2 mg/kg (maximum 90 mg) administered subcutaneously twice daily. In a second pediatric study of 25 children age 5–16 years, the 2 mg/kg dose, with a maximum dose of 90 mg, was found to yield drug concentrations similar to 60 mg/m^2 of body surface area dose and drug exposure was found to be independent of age group, body weight, body surface area, and sexual maturation *[6]*. Further data are needed in children <6 years of age. No metabolic induction or inhibition of enfuvirtide has been observed in PACTG 1005 or subsequent studies, nor was there a statistical relationship, within the utilized dosing schedule, between drug exposure with this agent and virologic benefit *[5]*.

Part B of PACTG 1005 evaluated the safety and antiretroviral activity of chronic twice-daily subcutaneous enfuvirtide administration at 60 mg/m^2 per dose in 14 children. For 7 days, the drug was added to each child's background antiretroviral regimen; at Day 7, the background regimen was optimized and enfuvirtide was continued, and children were followed for up to 96 weeks. Two children elected to discontinue enfuvirtide within 24 weeks (1 due to injection aversion, 1 due to an unrelated surgical procedure), 4 discontinued due to virologic failure (defined as >1 log increase in viral load above baseline), and 2 discontinued due to Grade 3 toxicity (thrombocytopenia, edema). In this cohort, most children had local injection site reactions. Seventy-nine percent of children had >0.7 log reduction in HIV RNA by Day 7. At 24 weeks of treatment, 71% had a >1.0 log reduction, 43% were suppressed to <400 copies/mL, and 21% were suppressed to <50 copies/mL *[4]*. However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at Week 96 *[3]*. Significant improvements in CD4 percentage and height *z* score were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase I/II study of enfuvirtide (2.0 mg/kg subcutaneously, maximum 90 mg, twice daily) plus an optimized background antiretroviral regimen enrolled 52 treatment-experienced children 3–16 years of age for 48 weeks. Of those completing 48 weeks of therapy (64%), the median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and there was a median increase of 106 cells/mm^3 (n = 25). Local skin reactions were common in all age groups (87%). Treatment responses at Week 8 were superior in younger (<11 years of age) children when contrasted with adolescents as measured by plasma HIV RNA change from baseline (-2.85 vs. -0.12 $\log_{10}$ copies/mL) or those maintaining HIV RNA <400 (42% vs. 4%). Median increases in CD4 count were 257 cells/mm^3 in children and 84 cells/mm^3 in adolescents. The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen *[1]*.

An increased rate of bacterial pneumonia was observed in adults treated with enfuvirtide compared with the control arm in the Phase III clinical trials *[7]*. A recent French cohort study with 1,220 patients receiving enfuvirtide and 9,374 patients on optimized therapy without enfuvirtide failed to find an increased risk of pneumonia *[8]*. Pediatric studies have not been powered to answer this question.

References

1. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J.* 2007;26(9):799-805.
2. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2002;21(7):653-659.
3. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2004;23(8):713-718.

4. Cunningham C, Church J, Hughes M, et al. Chronic subcutaneous T-20 (enfuvirtide) in HIV-infected children: 48 week outcome. 40th Annual Meeting of the Infectious Disease Society of America. October 24-27, 2002; Chicago, IL. Abstract 441.
5. Soy D, Aweeka FT, Church JA, et al. Population pharmacokinetics of enfuvirtide in pediatric patients with human immunodeficiency virus: searching for exposure-response relationships. *Clin Pharmacol Thera.* 2003;74(6):569-580.
6. Bellibas SE, Siddique Z, Dorr A, et al. Pharmacokinetics of enfuvirtide in pediatric human immunodeficiency virus 1-infected patients receiving combination therapy. *Pediatr Infect Dis J.* 2004;23(12):1137-1141.
7. Food and Drug Administration (FDA). Fuzeon package insert, revised December 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021481s017lbl.pdf.
8. Kousignian I, Launay O, Mayaud C, et al. Does enfuvirtide increase the risk of bacterial pneumonia in patients receiving combination antiretroviral therapy? *J Antimicrob Chemother.* 2010;65(1):138-144.

Maraviroc (MVC, Selzentry)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 150 mg and 300 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children <16 years.
No data currently available on dosage for children <16 years.

Adolescent (>16 years)/Adult dose:

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir [TPV/r])	150 mg twice daily
When given with NRTIs, enfuvirtide (ENF), TPV/r, nevirapine (NVP), raltegravir (RAL), and drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
When given with potent CYP3A inducers including efavirenz (EFV) and etravirine (ETR) (without a strong CYP3A inhibitor)	600 mg twice daily

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity
- Orthostatic hypotension

Special Instructions

- Conduct testing with HIV tropism assay prior to use to exclude the presence of CXCR4-using or mixed/dual tropic HIV.
- Can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism

- Cytochrome P450 (CYP) 3A4 substrate.
- Use caution when administering MVC to patients with hepatic impairment. Because MVC is metabolized by the liver, concentrations may be increased.
- No dosage recommendation in those with renal impairment, but patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if the potential benefits outweigh the risk.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Absorption:* Absorption of maraviroc is somewhat reduced with ingestion of a high fat meal; however, maraviroc can be given with or without food.
- *Metabolism:* Maraviroc is a cytochrome P450 (CYP) 3A4 and p-glycoprotein (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.
- *Less common (more severe):* Serious adverse events occurred in less than 2% of maraviroc-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**). Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Experience: The pharmacokinetics, safety, and efficacy of maraviroc in patients <16 years of age have not been established.

INTEGRASE INHIBITORS

Raltegravir (RAL, Isentress)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 400 mg (poloxamer tablet)

Dosing Recommendations	Selected Adverse Events
Neonate/Infant dose: Not approved for use in neonates/infants. **Pediatric dose:** Not approved for use in children <16 years of age. *Investigational dose in children ≥6 years of age (and >25 kg)*: 400 mg twice daily **Adolescent (≥16)/Adult dose:** 400 mg twice daily	• Nausea, diarrhea • Headache • Fever • CPK elevation **Special Instructions** • Can be given without regard to food. **Metabolism** • UGT1A1-mediated glucuronidation. • No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment. • No dosage adjustment is necessary in patients with renal impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- *Metabolism:* The major mechanism of clearance of raltegravir is mediated through glucuronidation by UGT1A1. Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir while inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting. In patients with chronic active hepatitis B and/or C, worsening of laboratory abnormalities from baseline AST, ALT, or total bilirubin is more likely than in patients not coinfected.
- *Rare:* Creatine phosphokinase elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash and Stevens-Johnson syndrome have been reported. Thrombocytopenia.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/cgi-bin/INIResiNote.cgi).

Pediatric Experience: The pharmacokinetics, safety, and efficacy of raltegravir in patients <16 years of age have not been established. Raltegravir in combination with other antiretrovirals is currently being evaluated in IMPAACT 1066, a Phase I/II study in HIV-infected children. The study objectives include selecting an age-appropriate pediatric dose approximating the exposure (AUC and C_{min}) achieved in adults treated with 400 mg twice daily. The intensive pharmacokinetic evaluations are performed on Day 7–12 after raltegravir is added to a stable antiretroviral backbone. After the pharmacokinetic specimens are obtained the backbone regimen is changed.

Initially, intensive PK evaluations were performed in children 12 to <19 years of age, with raltegravir administered with food because there is no food or fasting requirement with its licensed use in adults *[1]*. However, because the effect of food made comparisons to data obtained in fasting adults difficult, the study was then amended to conduct PK evaluations in the fasted state. This led to selection of a dose of 400 mg twice daily of the approved formulation (poloxamer tablet) in children ≥12 to <19 years of age for longer term evaluation of safety and efficacy *[2]*. Preliminary data from 43 participants in this age group after 24 weeks of treatment with raltegravir plus an optimized background regimen demonstrated that 71% had either a viral

load <400 copies/ml or a 1.0 log decrease in viral load; 53% had a viral load <50 copies/ml; and the median CD4 count increase was 111 cells/mm^3. There were 4 Grade 3 adverse reactions judged possibly related to raltegravir (2 neutropenic episodes, 1 liver enzyme elevation, and 1 behavioral change); no participants discontinued therapy due to toxicity *[3]*.

Children ≥6 to <12 years of age were initially treated at a dose of 8 mg/kg twice daily. Evaluation of the pharmacokinetic data in 10 participants again led to choosing a uniform dose of 400 mg twice daily for those with a weight >25 kg. At 12 and 24 weeks of therapy, 78% and 67% of 14 children in this cohort had a viral load <400 copies/ml *[4]*. No unusual toxicity has been seen so far *[4-5]*.

In addition to the approved adult formulation (poloxamer tablet) two investigational raltegravir preparations are being evaluated in IMPAACT 1066: a chewable ethylcellulose formulation in children >2 to <12 years of age *[6]* and an oral suspension for children <2 years of age.

References

1. Acosta A, Wiznia A, Nachman S, et al. Raltegravir (RAL) pharmacokinetics (PK) in adolescents: Preliminary results from IMPAACT protocol 1066. Paper presented at: 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2008; New Orleans, LA. Abstract P8.
2. Nachman S, Acosta E, Wiznia A, et al. Raltegravir phamacokinetics (PK) and safety in adolescents: Preliminary results from IMPAACT P1066. Paper presented at: 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); October 25-28, 2008; Washington, DC. Abstract H-4059A.
3. Nachman S, Samson P, Frenkel L, et al. 24 week safety and efficacy from IMPAACT P1066: A phase I/II, multicenter, open-label, noncomparative study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 12-15, 2009; San Francisco, CA. Abstract H-924a.
4. Nachman S, Samson P, Acosta E, et al. Pharmacokinetic (PK), safety, and efficacy data on cohort IIA; youth aged 6 to 11 years from IMPAACT P1066: A phase I/II study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 873.
5. Wiznia A, Samson P, Acosta E, et al. Safety and efficacy of raltegravir (RAL) in pediatric HIV infection. Preliminary Analysis from IMPAACT P1066. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 874.
6. Nachman S, Acosta E, Samson P, et al. Interim results from IMPAACT P1066: Raltegravir (RAL) oral chewable tablet (OCT) formulation in children 6 to 11 years. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 161LB.