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CD4+ T-cell count at antiretroviral therapy initiation in the "Treat All" era in South A: an interrupted time series analysis.

Yapa HM; Kim H-y; Post FA; Jiamsakul A; de Neve J-W ...

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Developed by the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

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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.

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What's New in the Pediatric Guidelines (Last updated November 5, 2012; last reviewed November 1, 2012)

Key changes made to update the August 11, 2011, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* are summarized below. Minor revisions have been made in toxicity tables and other sections of the document; all changes are highlighted throughout the guidelines. Throughout the document, references have been updated to include new publications where relevant.

Diagnosis of HIV infection

- New section on diagnostic testing in children with perinatal HIV exposure in exceptional situations: late seroreversion up to 24 months of age, postnatal exposure in children with prior negative virologic tests for whom there are additional HIV transmission risks (e.g., breastfeeding, feeding premasticated food), and non-subtype B HIV-1 infection and HIV-2 infection.
- New section on diagnostic testing in children with non-perinatal exposure.

When to Start Antiretroviral Therapy

- CD4 T lymphocyte (CD4 cell) count and CD4 percentage thresholds for initiation of treatment are now offered for children aged >12 months, but in the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.
- Although CD4 percentage had been preferentially used to monitor immunologic status in children aged <5 years, recent analyses show that CD4 cell counts provide greater prognostic value than CD4 percentage for short-term disease progression in children aged <5 years as well as in older children.
- CD4 thresholds for treatment have been further subdivided into age groups 1 to <3, 3 to <5, and ≥5 years to more precisely link them to age-related changes in absolute CD4 cell count.
- The Panel continues to recommend treatment of all HIV-infected infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load (**AI** for infants aged <12 weeks and **AII** for infants aged ≥12 weeks to 12 months).
- The Panel discusses current adult antiretroviral (ARV) guidelines and similarities and differences between children and adults. Adult guidelines have been modified to recommend treatment for all HIV-infected individuals, with the strength of the recommendation based on the pre-treatment CD4 cell count.
- In addition to recommending treatment for all children with AIDS or significant HIV-related symptoms **(AI*)**, the Panel also generally recommends treatment for all children aged ≥1 year with minimal or no symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection), with the strength of recommendation based on age and CD4 cell count/percentage. However, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.
    - ART should be initiated in HIV-infected children aged ≥1 year with minimal or no symptoms with the following CD4 values:
        - Aged 1 to <3 years:
            - With CD4 cell count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**
        - Aged 3 to <5 years:
            - With CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**

- Aged ≥5 years:
  - With CD4 cell count ≤500 cells/mm^3 (**AI*** for CD4 cell count <350 cells/mm^3, **BII*** for CD4 cell count 350–500 cells/mm^3)

- ART should be considered for HIV-infected children aged ≥1 year with minimal or no symptoms with the following CD4 values:
  - Aged 1 to <3 years:
    - With CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Aged 3 to <5 years:
    - With CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Aged ≥5 years:
    - With CD4 cell count >500 cells/mm^3 **(BIII)**
- In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment **(BII)**.

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

- Tenofovir disoproxil fumarate (tenofovir) has recently been FDA-approved for children as young as age 2 years. The Panel has modified its recommendations for use of tenofovir in children based on Tanner staging. Tenofovir, in combination with lamivudine or emtricitabine, is part of a Recommended nucleoside reverse transcriptase inhibitor (NRTI) combination for adolescents who are Tanner stage 4 or 5 **(AI*)**, an Alternative choice for those who are Tanner stage 3, and reserved for Special Circumstances for those aged ≥2 years and Tanner stage 1 or 2.
- Etravirine and rilpivirine are also FDA-approved but are not recommended as initial therapy at this time because of lack of experience and dosing information in children.
- Boosted fosamprenavir is now FDA-approved for infants as young as age 4 weeks, provided that they were born at ≥38 weeks' gestation. However, because of palatability and lower drug exposure in young infants, boosted fosamprenavir, when used in combination with 2 NRTIs, is an Alternative option only in infants and children aged 6 months and older.
- Darunavir with low-dose ritonavir is now FDA-approved and, when used in combination with 2 NRTIs, an Alternative regimen in children aged ≥3 years. Once-daily dosing of boosted darunavir in children aged <12 years is not recommended.
- Raltegravir is now FDA-approved for children aged ≥2 years, but are not recommended for initial therapy at this time because of insufficient data. Elvitegravir, another integrase inhibitor, is only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir, and is FDA-approved for HIV-1-infected ARV treatment-naive adults, but not children aged <18 years. Given the lack of data in individuals aged <18 years, it cannot be considered for use as initial therapy in children at this time.
- Although emerging information about the use of efavirenz in pregnancy is reassuring, the Panel awaits additional safety information and recommends that alternative regimens that do not include efavirenz be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise a woman's health **(BIII)**.

Management of Treatment-Experienced Infants, Children, and Adolescents

- Management of treatment failure has been more clearly limited to management of virologic treatment failure. There is no consensus on how to manage immunologic or clinical treatment failure in the absence of virologic treatment failure.
- Newer individual drugs and classes of ARV drugs have been incorporated into both the discussion and the table of new regimen options for children with treatment failure (Table 20).

Specific Issues in Adolescents

- Updates have been provided in the section on contraceptive and ARV drug interactions.
- An update was provided regarding pregnancy outcomes in adolescent girls.

Pediatric Antiretroviral Drug Information

Updates with new pediatric data are provided when relevant for specific drugs.

- **Emtricitabine:** The Panel provides neonatal pharmacokinetic (PK) data at a dose of 3mg/kg/day, and PK data in children indicating that the oral solution has 20% lower plasma exposure than the capsule formulation. Information is provided on Complera (fixed-dose combination of tenofovir, emtricitabine, and rilpivirine) for adolescents aged >18 years and adults.
- **Lamivudine:** The Panel provides information on generic tablet formulations and weight band dosing for children who weigh ≥14 kg, using 150-mg scored tablets. The Panel discusses switching from twice-daily to once-daily dosing at 8 to10 mg/kg, based on review of data from the PENTA 13 and 15 and ARROW trials.
- **Stavudine:** The Panel recommends a maximum dose of 30 mg of stavudine.
- **Tenofovir:** The Panel provides information on the newly available pediatric oral powder and tablets of lower milligram amounts (150, 200, and 250 mg), and dosing by weight band starting at age 2 years and 10 kg, with a discussion of the recommended pediatric dose of 8 mg/kg/dose once daily and results of the studies that led to registration of the drug. The Panel notes Truvada (emtricitabine/tenofovir) is now FDA-approved for use in adolescents aged ≥12 years and who weigh ≥35 kg; and Atripla (emtricitabine/tenofovir/efavirenz) is now FDA-approved for use in adolescents aged ≥12 years and who weigh ≥40 kg.
- **Zidovudine:** Dosing recommendations for zidovudine used as prophylaxis for prevention of mother-to-child HIV transmission and in infants have been updated.
- **Efavirenz:** Additional detail has been added involving the precaution against using efavirenz in women of childbearing potential.
- **Etravirine:** Pediatric dosing recommendations have been updated to reflect FDA approval for treatment-experienced children aged 6 to <18 years.
- **Nevirapine:** The Panel notes data showing a three-fold increased risk of rash and hepatotoxicity in children with CD4 percentage >15% when initiating nevirapine.
- **Rilpivirine:** The Panel notes the availability of Complera (fixed-dose combination of tenofovir, emtricitabine, and rilpivirine) for adolescents aged >18 years and adults. A pediatric trial is under way in treatment-naive adolescents aged 12 to 18 years. The Panel recommends that rilpivirine should be administered with a meal that contains at least 500 calories, and notes that rilpivirine should not be used with proton pump inhibitors.

- **Atazanavir:** Modifications have been made in the dosing table and new dosing recommendations are discussed.
- **Darunavir:** Additional dosing down to a weight of 10 kg and PK of this dosing by weight band are described. The caveat against darunavir use in children aged <3 years was strengthened and explained more fully: Do not use darunavir in children aged <3 years because of concerns related to seizures and death in infant rats due to immaturity of the blood-brain barrier and liver metabolic pathways.
- **Fosamprenavir:** The Panel added information on FDA approval in infants as young as 4 weeks but notes that the Panel does not recommend use in infants aged <6 months, given concerns about palatability and low drug level exposures. Details about PK have also been added and a dosing table was added for children aged 6 months to 18 years.
- **Lopinavir/ritonavir:** The Panel discusses a preference for dosing in children at 300 mg lopinavir/m^2 twice daily rather than 230 mg/m^2 twice daily, particularly for ARV-experienced patients.
- **Raltegravir:** Information has been added on the newly available pediatric chewable tablets (25 and 100 mg), dosing by weight band starting at age 2 years, and results from the trials that led to FDA approval in children are summarized.
- **Elvitegravir:** Information has been added on the newly available fixed-dose combination tablet containing the integrase strand transfer inhibitor elvitegravir plus the PK booster cobicistat and the NRTIs emtricitabine and tenofovir. The Panel notes there are no data on its use in individuals aged <18 years.

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Members of Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (Last updated November 1, 2012; last reviewed November 1, 2012)

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 Office of AIDS Research Advisory Committee (OARAC) and supported 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 L. Havens, MS, MD	Medical College of Wisconsin, Children's Hospital 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, Bethesda, MD
Members of the Panel:	
Elaine J. Abrams, MD	Columbia University, New York, NY
Allison Agwu, MD, SCM	Johns Hopkins School of Medicine, Baltimore, MD
Ben Banks, MPH, BSW	Ashland, VA
Edmund V. Capparelli, PharmD	University of California – San Diego, La Jolla, CA
Ellen G. Chadwick, MD	Northwestern University, Chicago, IL
Rana Chakraborty, MD, MS, PhD	Emory University School of Medicine, Atlanta, GA
Diana F. Clarke, PharmD	Boston Medical Center, Boston, MA
Patricia M. Flynn, MD	St. Jude Children's Research Hospital, Memphis, TN
Marc D. Foca, MD	Columbia University, New York, NY
Paul A. Krogstad, MD	University of California – Los Angeles, Los Angeles, CA
James B. McAuley, MD, MPH, DTM&H	Rush University Medical Center, Chicago, IL
Ann J. Melvin, MD, MPH	Seattle Children's Hospital, University of Washington, Seattle WA
Mark Mirochnick, MD	Boston University School of Medicine, Boston, MA
Paul Palumbo, MD	Geisel School of Medicine at Dartmouth, Lebanon, 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
Eva Janzen Powell, BA	Chicago, IL
Natella Rakhmanina, MD, PhD	Children's National Medical Center, Washington, DC
Theodore Dumont Ruel, MD	University of California – San Francisco, San Francisco, CA
Richard M. Rutstein, MD	Children's Hospital of Philadelphia, Philadelphia, PA
Dorothy Shaw, BA	Birmingham, AL

Members from the Department of Health and Human Services:	
Brian Feit, MPA	Health Resources and Services Administration, Rockville, MD
Rohan Hazra, MD	National Institutes of Health, Bethesda, MD
Patrick Jean-Philippe, MD	Henry Jackson M. Foundation-Division of AIDS, National Institutes of Health, Bethesda, MD
Linda Lewis, MD	Food and Drug Administration, Silver Spring, MD
George K. Siberry, MD, MPH	National Institutes of Health, Bethesda, MD
Allan W. Taylor, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Nonvoting Observer:	
Jason Brophy, MD, MSc, DTM&H	Children's Hospital of Eastern Ontario, Ottawa ON
Nonvoting Observers from the François-Xavier Bagnoud Center, School of Nursing, University of Medicine and Dentistry of New Jersey:	
Carolyn Burr, RN, EdD	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Deborah Storm, MSN, PhD	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ

HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (page 1 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Name	Panel Status	Company	Relationship
Abrams, Elaine J.	M	None	N/A
Agwu, Allison	M	None	N/A
Banks, Ben	M	None	N/A
Brophy, Jason	NVO	Abbott Labs	• Research Support
Capparelli, Edmund V.	M	Abbott Labs Cerexa Trius Therapeutics	• Advisory Board • Consultant • Consultant
Chadwick, Ellen G.	M	Abbott Labs Bristol-Myers Squibb GlaxoSmithKline Johnson & Johnson Merck Novartis Pfizer Roche Sanofi-Aventis	• Stockholder and stock options • Stockholder • Stockholder • Stockholder • Stockholder • Stockholder • Stockholder • Stockholder • Stockholder
Chakraborty, Rana	M	None	N/A
Clarke, Diana F.	M	None	N/A
Feit, Brian	HHS	None	N/A
Flynn, Patricia M.	M	Tibotec Merck Sharp & Dohme	• Research support • Consultant
Foca, Marc D.	M	None	N/A
Havens, Peter L.	C	None	N/A
Hazra, Rohan	HHS	None	N/A
Jean-Philippe, Patrick	HHS	None	N/A
Krogstad, Paul A.	M	None	N/A
Lewis, Linda	HHS	None	N/A
McAuley, James B.	M	None	N/A
Melvin, Ann J.	M	Gilead	• DSMB member
Mirochnick, Mark	M	Abbott Labs	• Advisory board member
Mofenson, Lynne	ES	None	N/A
Palumbo, Paul	M	None	N/A
Paul, Mary E.	M	None	N/A
Peters, Vicki B.	M	None	N/A
Powell, Eva Janzen	M	None	N/A

HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Name	Panel Status	Company	Relationship
Rakhmanina, Natella	M	Abbott Labs Bristol-Myers Squibb Pfizer	• Honoraria • Travel Support • Research Support • Research Support
Ruel, Theodore Dumont	M	None	N/A
Rutstein, Richard M.	M	None	N/A
Shaw, Dorothy	M	None	N/A
Siberry, George K.	HHS	None	N/A
Storm, Deborah	NVO	Eli Lilly and Company Merck Roche	• Stockholder • Stockholder • Stockholder and stock options (spouse is an employee)
Taylor, Allan W.	HHS	None	N/A
Van Dyke, Russell	C	Gilead	• Research Support
Weinberg, Geoffrey A.	C	GlaxoSmithKline Vaccines Merck Vaccines Sanofi Pasteur Vaccines	• Speaker's Bureau • Speaker's Bureau • Speaker's Bureau

C = Co-Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; HHS = Member from HHS; M = Member; N/A = Not applicable; NVO = Non-Voting Observer

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

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

Also available on the AIDS*info* website are separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children[1] and for the use of ARV agents in HIV-infected (postpubertal) adolescents and adults.[2] Because these guidelines are developed for the United States, they may not be applicable in other countries. The World Health Organization (WHO) provides guidelines for resource-limited settings at http://www.who.int/hiv/pub/arv/en.

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

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

- Acquisition of infection through perinatal exposure for most infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to ARV drugs in most perinatally infected children;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than age 18 months;
- Age-specific differences in interpreting CD4 T lymphocyte (CD4 cell) counts;
- Changes in pharmacokinetic (PK) parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
- Differences in the clinical manifestations and treatment of HIV infection secondary to onset of infection in growing, immunologically immature individuals; and

- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

These recommendations represent the current state of knowledge regarding the use of ARV drugs in children and are based on published and unpublished data regarding the treatment of HIV infection in infants, children, adolescents, and adults, and when no definitive data were available, on the clinical expertise of the Panel members. The Panel intends the guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.
Panel members	The Panel is composed of approximately 25 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the Panel Roster.
Financial disclosure	All members of the Panel submit a financial disclosure statement in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected infants, children, and adolescents
Developer	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC
Funding source	Office of AIDS Research, NIH and Health Resources and Services Administration
Evidence collection	A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the Francois-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	Described in Table 2.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals endorsed by a consensus of members are included in the guidelines as official Panel recommendations.

Guidelines Development Process

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

Topic	Comment
Other guidelines	These guidelines focus on HIV-infected infants, children, and adolescents through puberty. For more detailed discussion of issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of antiretroviral therapy (ART) in HIV-infected pregnant women and interventions for prevention of mother-to-child transmission (PMTCT), ART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website (http://aidsinfo.nih.gov).
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes.
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommendation includes a letter (**A**, **B**, or **C**) that represents the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that represents the quality of the evidence that supports the recommendation.

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

(1) The course of the disease and the effects of the drug in the pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients;

(2) Supplemental data exist on PKs of the drug in children indicating that systemic exposure in adults and children are similar; and

(3) Studies are provided that support the safety of the drug in pediatric patients.[7]

Studies relating activity of the drug to drug levels (pharmacodynamic data) in children also should be available if there is a concern that concentration-response relationships might be different in children.In many cases, evidence related to use of ARV drugs is substantially greater from adult studies (especially randomized clinical trials) than from pediatric studies. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

- **Quality of Evidence Rating I—Randomized Clinical Trial Data.**
  In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.

- Quality of Evidence Rating I will be used if there are data from large randomized trials in children with clinical and/or validated laboratory endpoints.

- Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. A rating of I* may be used for quality of evidence if, for example, a randomized Phase III clinical trial in adults demonstrates a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

- **Quality of Evidence Rating II—Nonrandomized Clinical Trials or Observational Cohort Data.** In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data may be used if there are sufficient pediatric data consistent with high-quality adult studies.

  - Quality of Evidence Rating II will be used if there are data from well-designed nonrandomized trials or observational cohorts in children.

  - Quality of Evidence Rating II* will be used if there are well-designed nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. A rating of II* may be used for quality of evidence if, for example, a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 cell count and data from smaller observational studies in children indicate that a similar CD4 count is associated with clinical benefit.

- **Quality of Evidence Rating III—Expert opinion.** The criteria do not differ for adults and children.

Table 2. Rating Scheme for Recommendations

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

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

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

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

- Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States.[8] Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy to both infected women and their infants and to reducing perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women, their HIV-exposed newborns, and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.‡
- The pharmaceutical industry and the federal government should continue collaborating to ensure that drug formulations suitable for administration to infants and children are available for all ARV drugs produced.
- Some information about the efficacy of ARV drugs for children can be extrapolated from clinical trials involving adults, but concurrent clinical trials in children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of Phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved ARV drug in children.
- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a specialist in pediatric and adolescent HIV infection. If that is not possible, such experts should be consulted.
- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families generally requires a multidisciplinary team approach that includes physicians, nurses, nutritionists, pharmacists, dentists, psychologists, social workers, child life specialists, and outreach workers.
- Health care providers contemplating use of ARV drugs to treat infants, children, or adolescents should consider certain factors that influence adherence to therapy, including:
    - availability and palatability of drug formulations;
    - impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food;
    - ability of the children's caregiver or the adolescents themselves to administer complex drug regimens and availability of resources that might be effective in facilitating adherence; and
    - potential for drug interactions.
- The choice of initial ARV regimen should include consideration of factors that may limit future treatment options, such as the presence of or potential for development of resistance to ARV drugs. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring of growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition is essential in the care of HIV-infected children because those factors may significantly influence quality of life.

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

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Identification of Perinatal HIV Exposure (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
• Repeat HIV testing in the third trimester should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection (such as those with a known HIV-infected partner, personal or partner history of injection drug use, diagnosis with a sexually transmitted disease [STD], signs or symptoms of acute HIV infection or who reside in a high-prevalence area) **(AIII)**.
• Rapid HIV antibody testing at the time of labor or delivery should be performed on women with undocumented HIV status, and intrapartum antiretroviral (ARV) prophylaxis should be initiated in those who test positive **(AII)**.
• For pregnant women who are suspected to have acute HIV infection, a virologic test such as a 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 before or during labor should undergo rapid HIV antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing. If results in mother or infant are positive, infant ARV prophylaxis should be initiated as soon as possible and the mothers should not breastfeed unless confirmatory HIV antibody testing is negative **(AII)**.
• Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
• Infant HIV antibody testing to determine HIV exposure should be considered for infants in foster care and adoptees for whom maternal HIV infection status is unknown **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*
† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

To treat HIV-infected infants appropriately, HIV-exposed infants must be identified as soon as possible, and that is best accomplished by identifying 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] All HIV testing should be performed in a manner consistent with state and local laws (http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws/). Centers for Disease Control and Prevention (CDC) recommends the "opt-out" approach, which involves notifying pregnant women that HIV testing will be performed as part of routine care unless they choose not to be tested for HIV.[7] The "opt-in" approach involves obtaining specific signed consent before testing and has been associated with lower testing rates. The mandatory newborn HIV testing approach involves testing of newborns for perinatal HIV exposure with or without maternal consent.[7]

Early identification of HIV-infected women is crucial for their health and for the care of their children, whether the children are infected or not. Knowledge of antenatal maternal HIV infection enables:

- HIV-infected women to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections for their own health;
- Provision of antiretroviral (ARV) 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 delivery to reduce perinatal transmission of HIV;[8-12]
- Counseling of HIV-infected women about the risks of HIV transmission through breast milk and that breastfeeding is not recommended for HIV-infected women living in the United States and other countries where safe alternatives to breast milk are available;[13]
- 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;[14] and
- Early diagnostic evaluation of HIV-exposed infants to permit early initiation of ART in infected infants.[2, 15]

Repeat HIV Testing in the Third Trimester

Repeat HIV testing should be considered for all HIV-seronegative pregnant women. It is recommended in the third trimester, preferably before 36 weeks' gestation, for women with initially negative HIV antibody tests who are at high risk of HIV infection.[16] A second HIV test during the third trimester is recommended for women who:

- Are receiving health care in a jurisdiction that has a high incidence of HIV or AIDS in women between ages 15 and 45 or are receiving health care in facilities in which prenatal screening identifies at least 1 HIV-infected pregnant woman per 1,000 women screened;
- Are known to be at high risk of acquiring HIV (such as those who are injection drug users or partners of injection drug users, exchange sex for money or drugs, are sex partners of HIV-infected persons, have had a new or more than 1 sex partner during current pregnancy, or have been diagnosed with a new sexually transmitted disease during pregnancy); or
- Have signs or symptoms of acute HIV infection.[5, 6, 17]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. There is evidence that for women, the risk of HIV acquisition is significantly higher during pregnancy than in the postpartum period.[18] If acute HIV infection is suspected, virologic testing with a plasma HIV RNA assay or other virologic assay should be performed because serologic testing may be negative at this early stage of infection.[19]

Rapid HIV Testing During Labor in Women with Unknown HIV Status

Use of rapid test kits or an expedited enzyme-linked immunosorbent assay (ELISA) to detect HIV antibodies is recommended to screen women seen at labor whose HIV status is undocumented and identify HIV exposure in their infants.[2, 5, 6, 15] Any hospital offering intrapartum care should have rapid HIV testing available and should have in place policies and procedures to ensure that staff are prepared to provide patient education about rapid HIV testing, that appropriate ARV medications are available whenever needed, and that follow-up procedures are in place for women found to be HIV-infected and their infants. Rapid tests have been found to be feasible, accurate, timely, and useful both in ensuring prompt initiation of intrapartum and neonatal ARV prophylaxis and in reducing perinatal transmission of HIV.[20] Results of rapid tests can be obtained within minutes to a few hours

and are as accurate as standard ELISA antibody testing.[21, 22] A positive rapid HIV test result must be followed by a confirmatory test such as a Western blot or immunofluorescent antibody (IFA) assay; a standard ELISA should not be used as a confirmatory test for a rapid HIV antibody test.[22] A single negative rapid test does not need confirmation unless acute HIV infection is suspected, in which case, a virologic test is necessary.[19] Immediate initiation of ARV prophylaxis for prevention of mother-to-child transmission (PMTCT) of HIV is strongly recommended pending confirmation of an initial positive rapid HIV test.[2, 4, 8, 15]

HIV Counseling and Testing During the Postnatal Period

Women who have not been tested for HIV before or during labor should be offered rapid testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing, with maternal counseling and consent unless state law allows testing without consent.[2, 6, 8, 15] Use of rapid HIV antibody assays or expedited ELISA for prompt identification of HIV-exposed infants is essential because neonatal ARV chemoprophylaxis should be initiated as soon as possible after birth—and no more than 12 hours later—to be effective for PMTCT.[23, 24] When an initial rapid test is positive in mother or infant, initiation of infant ARV prophylaxis and counseling against initiation of breastfeeding is strongly recommended pending results of confirmatory tests.[8] If the confirmatory test is negative and acute HIV infection is excluded, infant ARV prophylaxis can be discontinued and breastfeeding can be initiated. Mechanisms should be developed to facilitate rapid HIV screening for infants who have been abandoned and are in the custody of the state.

Infant HIV Testing When Maternal HIV Test Results Are Unavailable

When maternal HIV test results are unavailable (such as for infants who are in foster care)[25] or their accuracy cannot be evaluated (such as for infants adopted from a different country whose results are not reported in English), HIV antibody testing is indicated to identify HIV exposure in the infant. If antibody testing is positive, further testing is needed to diagnose HIV infection (see Diagnosis of HIV infection in Infants).

Acute Maternal HIV Infection During Pregnancy Or Breastfeeding

The risk of mother-to-child HIV transmission is increased in infants born to women who have acute HIV infection during pregnancy or lactation.[26-28] When acute retroviral syndrome is suspected in pregnancy or during breastfeeding, maternal testing should include a plasma HIV RNA test in addition to an HIV antibody test, because HIV antibody testing may be negative in early maternal infection. Women with suspected acute HIV infection who are breastfeeding should stop breastfeeding until HIV infection is confirmed or excluded. Pumping and temporarily discarding breast milk can be recommended and, if HIV infection is excluded, breastfeeding can resume. Care of pregnant or breastfeeding women and their infants identified with acute or early HIV infection should follow guidelines in *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*.[8]

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Diagnosis of HIV Infection in Infants and Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months **(AII)**.
- Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months **(AII)**.
- Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection **(BIII)**.
- HIV DNA polymerase chain reaction and HIV RNA assays are recommended as preferred virologic assays **(AII)**.
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
- Definitive exclusion of HIV infection in nonbreastfed infants 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 **(AII)**.
- Some experts confirm the absence of HIV infection at 12 to 18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
- HIV antibody assays alone can be used for diagnosis of HIV infection in children with perinatal exposure who are ≥18 months of age and in children with non-perinatal exposure (see text for exceptions) **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Diagnostic Testing in Infants with Perinatal HIV-1 (HIV) Exposure

HIV infection can be definitively diagnosed through use of virologic assays in most nonbreastfed HIV-exposed 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 to HIV; therefore a virologic test should be used.[1, 2] A positive virologic test (that is, detection of HIV by DNA polymerase chain reaction (PCR) or RNA assays) indicates likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen because false-positive results can occur with both RNA and DNA assays.

HIV culture is not used for routine HIV diagnostic testing, although it has a sensitivity similar to that of HIV DNA PCR.[3] It is more complex and expensive to perform than DNA PCR or RNA assays and may require 2 to 4 weeks for definitive results; it is generally not available outside of research laboratories. 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.[4, 5]

An infant who is found to have positive HIV antibody on screening but whose mother's HIV status is unknown (see Identification of Perinatal HIV Exposure), should be assumed to be HIV-exposed and undergo the HIV diagnostic testing described here.

HIV DNA PCR

HIV DNA PCR is a sensitive technique used to detect specific HIV viral DNA in peripheral blood mononuclear cells (PBMCs). The specificity of the HIV DNA PCR is 99.8% at birth and 100% at 1, 3, and 6 months. The sensitivity of the test performed at birth is 55% but increases to more than 90% by 2 to 4 weeks of age, and 100% at 3 months and 6 months of age.[6-8]

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in the plasma. Their specificity (for results ≥5,000 copies/mL) has been shown to be 100% at birth, 1, 3, and 6 months of age and is comparable to HIV DNA PCR.[8] HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant. The sensitivity of HIV RNA assays has been shown to be 25% to 58% during the first weeks of life, 89% at 1 month of age, and increases to 90% to 100% by 2 to 3 months of age.[6-11] HIV RNA assays are as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. 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). It is established that HIV DNA PCR remains positive even in individuals receiving highly active antiretroviral therapy (HAART).[12] However, RNA assays can be affected by maternal antenatal therapy with combination antiretroviral (ARV) drugs and/or infant ARV prophylaxis. Among a group of 47 infants who received zidovudine prophylaxis, HIV RNA levels were lower at 1 month of age compared with levels at 3 months of age (median of 5.1 vs. 5.6 logs) and among 9 infants who received combination ARV prophylaxis, the median was 2.5 logs at 1 month of age. However, prenatal and neonatal combination ARV regimens did not affect the sensitivity of the assay to detect the presence of HIV.[8]

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing.[13-17]

Issues Related to Diagnosis of Non-Subtype B HIV-1 Infections

Although HIV-1 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.[18-20] Currently available HIV DNA PCR tests have decreased sensitivity for detection of non-subtype B HIV, and false-negative HIV DNA PCR test results have been reported in infants infected with non-subtype B HIV.[21-24] 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.[25]

Some currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection,[26-31] although even these assays may not detect or properly quantify some non-B subtypes, particularly the more uncommon group O HIV subtypes.[28, 32, 33]

When evaluating an infant whose mother or father (or both) 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.[28, 34] In addition, when non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR results, repeat testing using one of the newer RNA assays is recommended. In these situations, the clinician should consult with an expert in pediatric HIV infection. The child should undergo close clinical monitoring and HIV serologic testing at age 18 months to definitively rule out HIV infection.

Issues Related to Diagnosis of HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique;West African countries including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and in parts of India.[35, 36] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions;[37] HIV-2 is rare in the United States. HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic, who are HIV-1 antibody positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot and HIV-1 RNA viral loads at or below the limit of detection.[38] This pattern of HIV testing can also be seen in patients who have a false-positive HIV-1 test. HIV-1 and HIV-2 coinfections may also occur further complicating the diagnosis.

The majority of commercially available HIV screening antibody tests can detect both HIV-1 and HIV-2 but cannot distinguish between the two viruses. The only Food and Drug Administration (FDA)-approved antibody test that distinguishes between HIV-1 and HIV-2 is the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test. If HIV-2 is suspected, infection can be confirmed using a supplemental test such as an HIV-2 immunoblot or HIV-2-specific Western blot. HIV-2 immunoblots are available through commercial labs; however, none are FDA-approved for HIV-2 diagnosis. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by the Centers for Disease Control and Prevention.

Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays (HIV-2 DNA PCR testing) at time points similar to those used for HIV-1 testing. HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (1-888-448-8765) can provide a list of sites that perform this testing. Clinicians should consult with an expert in pediatric HIV infection if caring for infants with suspected or known exposure to HIV-2.[36, 39, 40]

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 to 21 days, at age 1 to 2 months, and at age 4 to 6 months. Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection (see below).

Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples, regardless of a child's age. A positive HIV antibody test with confirmatory Western blot (or immunofluorescent antibody [IFA] assay) at age ≥18 months confirms HIV infection, except in rare late seroreverters (see Diagnostic Testing in Exceptional Situations section below).[1]

HIV infection can be *presumptively* excluded in non-breastfed infants with two or more negative virologic tests, with one test obtained at ≥14 days of age and one obtained at ≥4 weeks of age, or one negative virologic test obtained at ≥8 weeks of age, or one negative HIV antibody test obtained at ≥6 months of age.[1, 41] *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at 4 to 6 weeks of age until they are determined to be HIV uninfected or *presumptively* uninfected with HIV.[42, 43] Thus, initiation of PCP prophylaxis can be avoided or, if prophylaxis was initiated, can be stopped, if an infant has negative virologic tests at 2 weeks of age and at ≥4 weeks of age, or if virologic

testing is negative at ≥8 weeks of age.

Definitive exclusion of HIV infection in a non-breastfed infant is based on 2 or more negative virologic tests, with one obtained at ≥1 month of age and one at ≥4 months of age, or 2 negative HIV antibody tests from separate specimens obtained at ≥6 months of age. For both *presumptive* and *definitive* exclusion of HIV infection, a child must have no other laboratory (meaning, no positive virologic test results or low CD4 T lymphocyte [CD4 cell] count/percent) or clinical evidence of HIV infection and not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at 12 to 18 months of age to document seroreversion to HIV antibody negative status.

Virologic Testing at Birth (Optional)

Virologic testing at birth can be considered for newborns at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal antiretroviral therapy (ART), were diagnosed with acute HIV infection during pregnancy, or who had HIV viral loads ≥1,000 copies/mL close to the time of delivery. As many as 30% to 40% of HIV-infected infants can be identified by 48 hours of age.[7] Blood samples from the umbilical cord should not be used for diagnostic evaluations because of the potential for 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 (that is, 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 (that is, intrapartum) infection.[44] 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.[44, 45] 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.[46] 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.[46]

Virologic Testing at Age 14 Days to 21 Days

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

Virologic Testing at Age 1 to 2 Months

Infants with negative virologic tests before 1 month of age should be retested at 1 to 2 months of age. Most HIV-exposed neonates will receive 6 weeks of neonatal ARV prophylaxis. Although ARV agents, in theory, could affect the predictive value of HIV virologic testing in neonates, use of prenatal/intrapartum/neonatal zidovudine single-drug prophylaxis did not delay detection of HIV by culture in infants in Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 and has not decreased the sensitivity and predictive values of many virologic assays.[9-11, 41, 47, 48] In one study, prenatal and neonatal combination ARV regimens lowered HIV RNA levels for HIV-exposed infected infants but did not affect the assay's sensitivity for detecting the presence of HIV (that is, HIV RNA levels remained detectable).[8] Further studies are necessary to confirm this finding. 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 PCP prophylaxis, assuming the child has no laboratory (such as, no positive virologic test results or low CD4 cell count) or clinical evidence of HIV infection.

Virologic Testing at Age 4 to 6 Months

HIV-exposed children who have had negative virologic assays at 14 to 21 days of age and at 1 to 2 months of age, have no clinical evidence of HIV infection, and are not breastfed should be retested at 4 to 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 in non-breastfed infants 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 to 18 Months to Document Seroreversion

If there has not been previous confirmation of two negative antibody tests, many experts confirm the absence of HIV infection in infants with negative virologic tests by repeat serologic testing between 12 and 18 months of age to confirm that maternal HIV antibodies transferred *in utero* have disappeared. The proportion of infants who serorevert by 15 to 18 months of age is close to 100%, with as many as 95% seroreverting by 12 months of age. Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.[1, 49-52]

Diagnostic Testing in Children with Perinatal HIV Exposure in Exceptional Situations

- Late seroreversion up to 24 months of age
- Postnatal HIV infection in HIV-exposed children with prior negative virologic tests for whom there are additional HIV transmission risks
- HIV-2 and non-subtype B HIV-1

On rare occasions, non-breastfed perinatally HIV-exposed infants with no other HIV transmission risk and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies for up to 24 months (these infants are called late seroreverters).[52-54] These children may have positive enzyme-linked immunosorbent assay (EIA) results but indeterminate confirmatory antibody tests (Western Blot or IFA). In such cases, repeat antibody testing at a later time would document seroreversion.

In contrast to late seroreverters, in rare situations, postnatal HIV infections have been reported in HIV-exposed infants who had prior negative HIV virologic tests. This occurs in infants who become infected through an additional risk after completion of testing (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure section below). If a confirmatory HIV antibody test is positive at 18 months of age, repeated virologic testing will distinguish between residual antibodies in uninfected, late seroreverting children and true infection.

Postnatal HIV exposure can occur if an HIV-infected mother breastfeeds her infant. Typical scenarios in the US include women who have not been adequately counseled about infant feeding, women who breastfeed despite being counseled not to do so, and women who learn of their HIV diagnosis only after initiating breastfeeding. Diagnostic testing to rule out acquisition of HIV through breast milk will only be accurate after breastfeeding has completely ceased. The timing of testing in such situations is discussed below in Diagnostic Testing in Children with Non-Perinatal HIV Exposure.

Another example where there can be postnatal HIV exposure is when an HIV-infected caregiver premasticates or prechews solid food before feeding it to an infant. This practice has been documented to result in HIV transmission.[53, 54] In such exposed children, both screening EIA and confirmatory antibody tests (EIA, Western Blot or IFA) may be positive at 18 months. Another study documented very rare cases of late postnatal infection without identified risk factors, suggesting the possibility of intrafamilial HIV transmission.[55]

Children with non-subtype B HIV-1 infection and children with HIV-2 infection may have persistent positive EIA tests and indeterminate confirmatory antibody tests.[21-24] Situations in which such infections may be suspected and the diagnostic approach to them are discussed above in the sections Issues Related to Diagnosis of Non-Subtype B Infection and Issues Related to Diagnosis of HIV-2 Infection.

Diagnostic Testing in Children with Non-Perinatal HIV Exposure

Breastfeeding is a known route of HIV transmission. Infants who are breastfed by an HIV-infected woman, including those diagnosed with acute HIV infection during breastfeeding or who breastfed before knowing their HIV diagnosis, should undergo immediate HIV virologic testing and breastfeeding should be discontinued. Follow-up virologic testing should be performed at 4 to 6 weeks, 3 and 6 months after breastfeeding cessation if the initial tests are negative.[56] HIV antibody testing of an infant to assess for HIV exposure would not be helpful if the mother acquired HIV infection after giving birth. In that situation, an infant would be HIV antibody-negative but still at risk of acquiring HIV infection through breastfeeding and counseling to cease breastfeeding should be provided.

Perinatal HIV acquisition accounts for the majority of HIV infections in children, but providers may need to evaluate children exposed to HIV through other routes, such as sexual abuse, or because they were adopted from countries in which parenteral exposure to HIV via contaminated blood products is a possibility. In such cases, maternal HIV status may be negative or unknown. Receipt of solid food premasticated or prechewed by an HIV-infected caregiver also has been documented to be associated with risk of HIV transmission.[53, 54] Finally, acquisition of HIV is possible through accidental needle sticks or behavioral risks, such as sexual activity or injection drug use in older children.

HIV antibody testing should be performed on children who are suspected to have HIV infection because of clinical or laboratory findings consistent with HIV. Additional virologic testing may be necessary if acute HIV infection or end-stage AIDS is suspected because antibody testing can be negative in these situations.

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Laboratory Monitoring of Pediatric HIV Infection Prior to Therapy Initiation (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or CD4 T lymphocyte (CD4 cell) count and plasma HIV RNA level **(AII)**. For any given CD4 percentage and count, younger children, especially those in the first year of life, face higher risk of progression than do older children **(AII)**.
- In children younger than 5 years of age, CD4 percentage is generally preferred for monitoring immune status because of age-related changes in absolute CD4 cell count in this age group although absolute CD4 count may also be used **(AII)**.
- CD4 percentage and/or CD4 cell count should be measured at the time of diagnosis of HIV infection and at least every 3 to 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 to 4 months thereafter **(AIII)**.
- More frequent CD4 cell and plasma HIV RNA monitoring should be considered in children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Immunologic Monitoring in Children

Clinicians interpreting CD4 T lymphocyte (CD4 cell) counts in children must consider age as a factor. CD4 cell count and percentage values in healthy infants who are HIV-uninfected 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 age 5 years, the absolute CD4 cell count tends to vary more with age than does CD4 percentage. Therefore, in HIV-infected children younger than age 5 years, CD4 percentage has generally been preferred for monitoring immune status, whereas absolute CD4 cell count has been the preferred option and is used for children ≥5 years and can be used in younger children if CD4 percentage is not available.[3-5] However, an analysis from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) found that CD4 percentage provided little or no additional prognostic value compared with absolute CD4 cell regarding short-term disease progression in children <5 years as well as in older children.[6] Therefore, the pediatric guidelines include CD4 cell count thresholds as well as CD4 percentage thresholds for initiation of treatment in all children >12 months of age. In the case of discordance between CD4 percentage and absolute CD4 cell count, treatment decisions should be based on the lower value.[6]

In HIV-infected children, as in infected adults, the CD4 cell 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 every 3 to 4 months thereafter. Less frequent monitoring has been proposed for adults with high CD4 cell counts, but this has not been modeled for children in whom the risk of disease progression may differ substantially.[7] More frequent evaluation may be needed for children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy. Because of the risk of rapid progression, initiation of antiretroviral therapy (ART) is now recommended for all HIV-infected infants younger than age 12 months[8, 9] (see When to Initiate Therapy in Antiretroviral-Naive Children).

The prognostic value of CD4 percentage and HIV RNA copy number was assessed in a large individual patient meta-analysis (HPPMCS), 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 dying 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 dying 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 age 5 years or older was similar to that observed in young adults, with an increase in the risk of mortality when CD4 cell count fell below 350 cells/mm^3 (Table 4 and Figure 3).[3, 10]

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 a 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 aged 5 years 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 HPPMCS, there were no deaths among children 5 years of age or older with CD4 cell counts >350 cells/mm^3, although in younger children there continued to be a significant risk of death even with CD4 cell counts >500 cells/mm^3 (Table 4).

These risk profiles form the rationale for recommendations on when to initiate therapy in a treatment-naive HIV-infected child (see When to Initiate Therapy in Antiretroviral-Naive Children). A website using the meta-analysis from the HPPMCS is available to estimate the short-term risk of progression to AIDS or death in the absence of effective ART according to age and the most recent CD4 percentage/absolute CD4 cell count 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 cell count and percentage, thus, CD4 values are best measured when patients are clinically stable. No decision about 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 to 3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6 to 12 months after acute infection.[11, 12] In infected adults, the viral set point correlates with the subsequent risk of disease progression or death.[13]

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] In addition, 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]

HIV RNA levels (i.e., >299,000 copies/mL) in infants younger than 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] RNA levels (that is, >100,000 copies/mL) in older children also have 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 HPPMCS (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, 22]

HIV RNA copy number should be assessed as soon as possible after a child has a positive virologic test for HIV and every 3 to 4 months thereafter; more frequent evaluation may be necessary for children experiencing virologic, immunologic, or clinical deterioration or to confirm an abnormal value (see Management of Treatment-Experienced Infants, Children, and Adolescents).

Note that it is recommended that genotypic resistance testing be obtained before initiating ART and it is often performed in this monitoring period before a child qualifies for therapy (see Monitoring of Children on Antiretroviral Therapy).

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays

The use of HIV RNA assays for clinical purposes requires specific considerations,[23] which are discussed more completely elsewhere.[24] Several different methods can be used for quantitating HIV RNA, each of which 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 $\log_{10}$ copies/mL) or more.[25, 26]

Six Food and Drug Administration (FDA)-approved viral load assays using one of four different methodologies currently exist:

- HIV-1 reverse transcriptase (RT) quantitative polymerase chain reaction (PCR) assays: the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics), for which the lower limit of quantification differs between the "ultrasensitive" assay (<50 copies/mL) and the "regular sensitivity" assay (<400

copies/mL); the AmpliPrep/TaqMan HIV-1 Test, including the COBAS automated format (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);
- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (VERSANT Quantiplex HIV-1 RNA 3.0 Assay, Bayer Corporation); and
- Aptima HIV-1 RNA Qualitative assay (Gen-Probe Inc., San Diego, CA), primarily used for HIV diagnosis, as well as detection of less than full viral suppression during therapy.

The lower limits of quantification 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 is recommended to confirm that ART is producing maximal suppression of viremia. Because of the variability among assays in techniques and quantitative HIV RNA measurements, if possible, a single HIV RNA assay method should be used consistently to monitor an individual patient.[27, 28]

The predominant virus subtype in the United States is subtype B—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.[27, 31-35] It is particularly relevant for children who are born outside the United States or to foreign-born parents. 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 blood (100 µL of plasma), followed by the RT-PCR assays such as the Amplicor HIV-1 Monitor (200 µL of plasma) and 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 $\log_{10}$ copies/mL) in either direction over the course of a day or on different days.[21, 24, 26] 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 to 24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ copies/mL per year; a slower decline continues until approximately 4 to 5 years of age (average decline of 0.3 $\log_{10}$ copies/mL per year).

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

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;362:1605-1611.

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

	Absolute CD4 Cell Count (cells/mm^3)					
Age (Years)	**<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

Table modified 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[a]

		Deaths[b]	
Baseline HIV RNA[c] (copies/mL) / Baseline CD4 T-cell percentage	**No. Patients[d]**	**No.**	**(%)**
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

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

[b] Mean follow-up: 5.1 years.

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

[d] 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):1029–1038.

Figure 1. Estimated Probability of AIDS Within 12 Months of Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

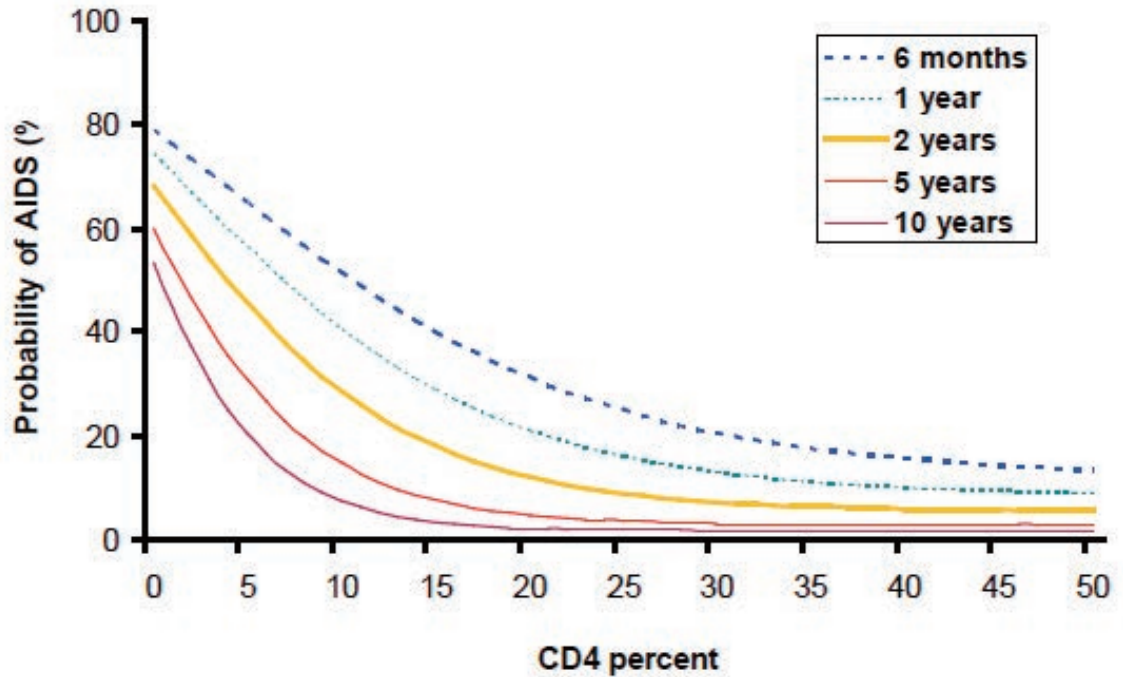


Table modified from: *Lancet* 2003;362:1605-1611

Figure 2. Estimated Probability of Death Within 12 Months of Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

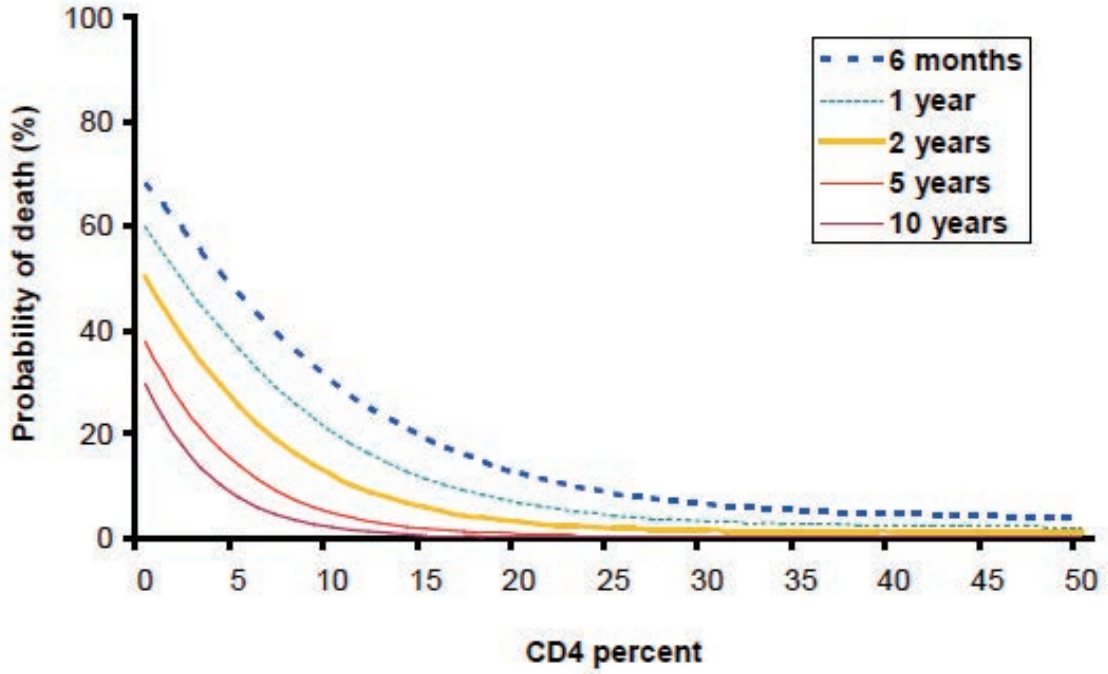


Table modified from: *Lancet* 2003;362:1605-1611

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

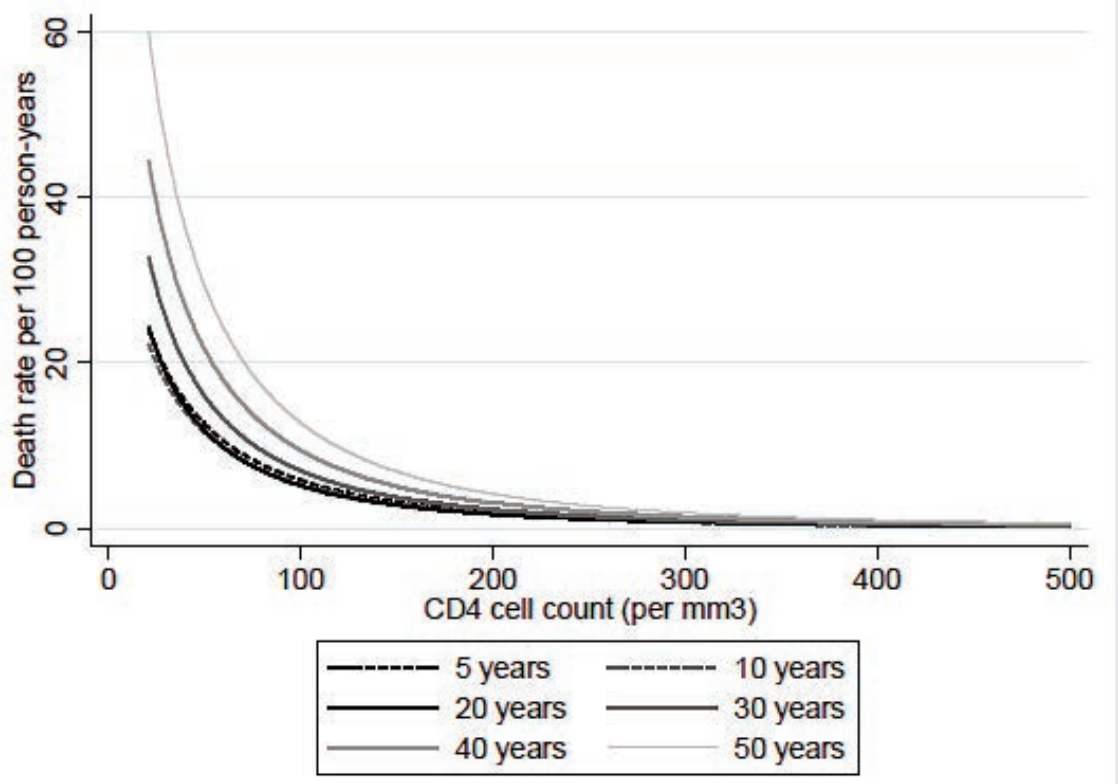


Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

Figure 4. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

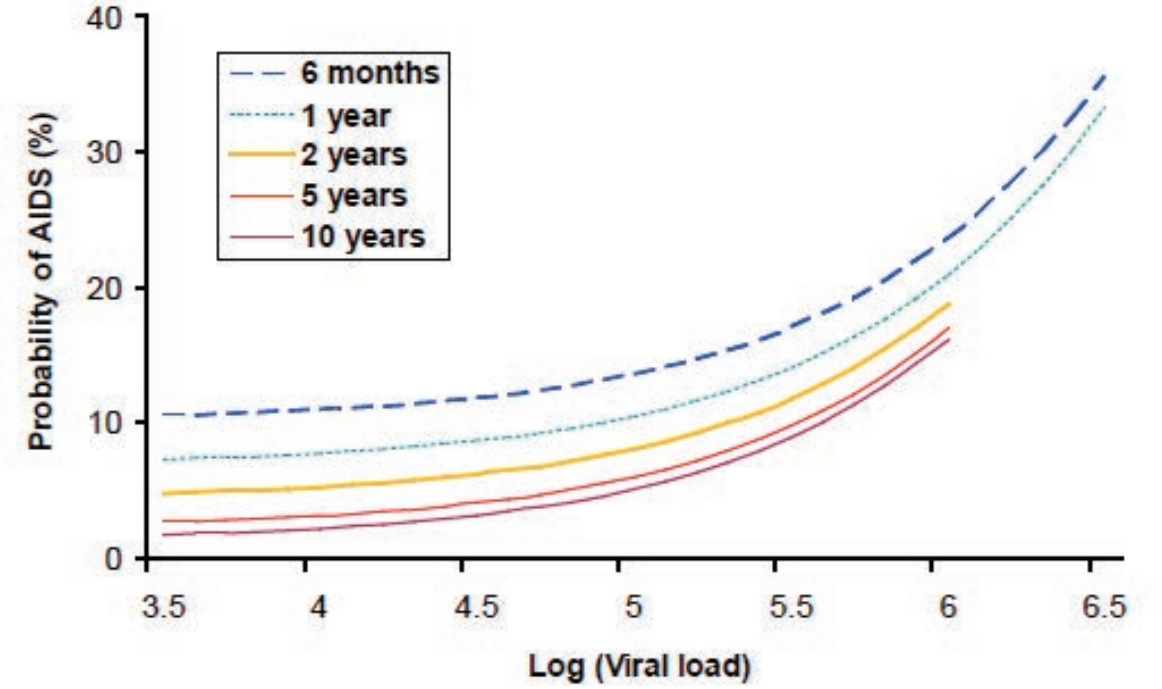


Table modified from: *Lancet* 2003;362:1605-1611

Figure 5. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

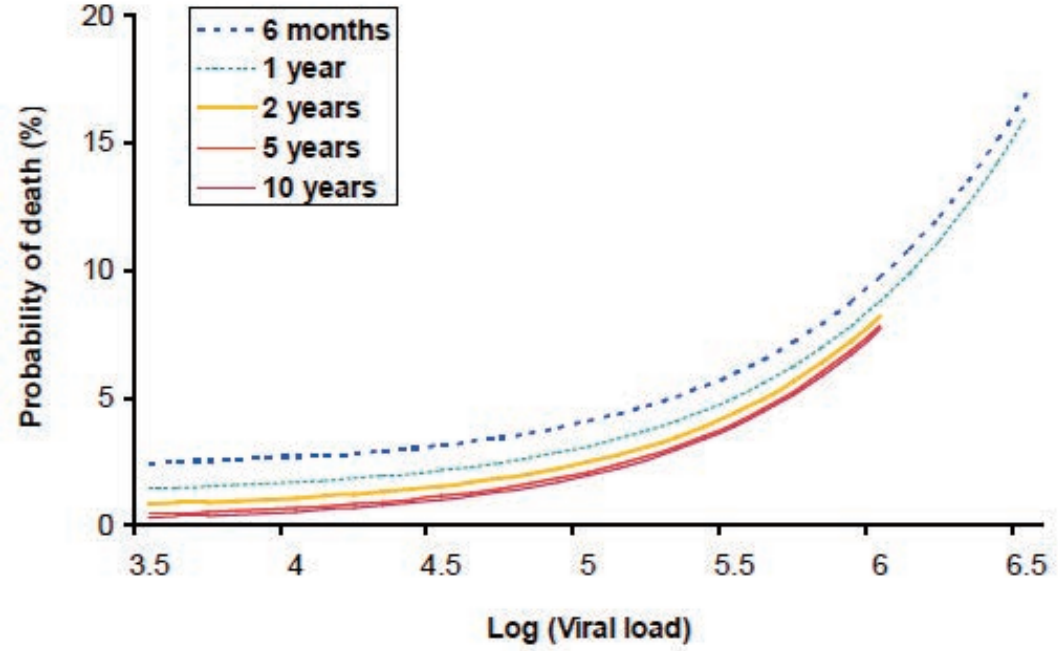


Table modified from: *Lancet* 2003;362:1605-1611

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Treatment Recommendations (Last updated November 1, 2012; last reviewed November 1, 2012)

General Considerations

Antiretroviral (ARV) treatment of pediatric HIV infection has steadily improved with the introduction of potent combination drug regimens that effectively suppress viral replication in most patients, resulting in a lower risk of failure due to development of drug resistance. Currently, combination regimens including at least three drugs from at least two drug classes 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.[1-5] 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;[6-8] significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period.[4, 7]

The increased survival of HIV-infected children is associated with challenges in selecting successive new ARV drug regimens. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be recognized in children.[9-11] (See Management of Medication Toxicity or Intolerance and Table 17.)

ARV drug-resistant virus can develop during combination antiretroviral therapy (ART) because of poor adherence, a regimen that is not potent, or a combination of these factors which results in incomplete viral suppression. Additionally, primary drug resistance may be seen in ARV-naive children who have become infected with a resistant virus.[12, 13] Thus, decisions about when to start therapy and what drugs to choose in ARV-naive children and on how to best treat ARV-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 ARV-naive children (when and what to start), when to change therapy, and treatment of ARV-experienced children will be discussed in separate sections of the guidelines.

Several factors need to be considered in making decisions about initiating and changing ART 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),[14, 15] degree of CD4 T lymphocyte (CD4 cell) immunosuppression, and level of HIV plasma viremia;
- availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child's age group;
- potency, complexity (such as dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the ARV regimen;
- effect of initial regimen choice on later therapeutic options;
- a child's ART history;
- presence of ARV drug-resistant virus;
- presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect drug choice;
- potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a 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 ARV drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting PK and safety data from Phase I/II trials in children. In addition, 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 ART does not eradicate HIV infection because of the long half-life of latently infected CD4 cells;[16-18] 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).[19] Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of ART for HIV-infected children and adolescents include:

- reducing HIV-related mortality and morbidity;
- restoring and/or preserving immune function as reflected by CD4 cell measures;
- maximally and durably suppressing viral replication;
- preventing emergence of viral drug-resistance mutations;
- minimizing drug-related toxicity;
- maintaining normal physical growth and neurocognitive development;
- improving quality of life; and
- reducing the risk of sexual transmission to discordant partners in adolescents who are sexually active.

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

Use and selection of ART: The treatment of choice for HIV-infected children is a regimen containing at least three drugs from at least two classes of ARV drugs. The Panel has recommended several preferred and alternative regimens (see What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children). The most appropriate regimen for an individual child depends on multiple factors as noted above. A regimen that is characterized as an alternative choice may be a preferred regimen for some patients.

Drug sequencing and preservation of future treatment options: The choice of ARV treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in ARV drug regimens can rapidly exhaust treatment options and should be avoided. 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. Current recommendations for initial therapy are to use two classes of drugs (see What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children), thereby sparing three classes of drugs for later use.

Maximizing adherence: As discussed in Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents, poor adherence to prescribed regimens can lead to subtherapeutic levels of ARV medications, which enhances the risk of development of drug resistance and likelihood of virologic failure. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with a child's caregiver and the child (when age appropriate) before the decision to initiate therapy is made. Participation by the caregiver and child

in the decision-making process is crucial. Potential problems should be identified and resolved before starting therapy, even if this delays initiation of therapy. In addition, frequent follow-up is important to assess 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 ARV regimen.

Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 1 of 2)

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 g/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 (that is, thrush) persisting for >2 months in children aged >6 months • Cardiomyopathy • Cytomegalovirus infection with onset before age 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (that is, more than two episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month • Herpes zoster (that is, 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 (that is, complicated chickenpox)

Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 2 of 2)

Category C: Severely Symptomatic

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

- Serious bacterial infections, multiple or recurrent (that is, 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 aged <2 years); 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 aged >1 month
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt), 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 jirovecii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at age >1 month
- 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 (such as 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 (that is, ≥ 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.

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When to Initiate Therapy in Antiretroviral-Naive Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Overview

The decision on when to initiate antiretroviral therapy (ART) in asymptomatic HIV-infected older children, adolescents, and adults continues to generate controversy among HIV experts. Aggressive therapy in the early stages of HIV infection has the potential to control viral replication before the evolution of HIV in that individual into a diverse and potentially more pathogenic quasispecies. Initiation of therapy at higher CD4 T lymphocyte (CD4 cell) counts has been associated with fewer drug resistance mutations at virologic failure in adults.[1] Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression.[2] Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of replication may reduce the occurrence of these non-AIDS complications.[2-8] In addition, data from a large randomized multinational clinical trial of HIV-serodiscordant adults demonstrated that effective ART reduced secondary transmission to an uninfected sexual partner by 96%.[9] Conversely, 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, improved adherence to the therapeutic regimen because the patient is symptomatic, and reduced or delayed adverse effects of ART. Because therapy in children is initiated at a young age and will likely be lifelong, concerns about adherence and toxicities are particularly important.

The Health and Human Services (HHS) Adult and Adolescent Antiretroviral Guidelines Panel now recommends initiation of therapy for all adults with HIV infection, with the proviso that the strength of the recommendations is dependent on the pre-treatment CD4 cell count.[10] Randomized clinical trials have provided definitive evidence of benefit with initiation of therapy in adults with CD4 cell counts <350 cells/mm^3.[11] Observational cohort data have demonstrated the benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm^3 in reducing morbidity and mortality; therefore, adult treatment guidelines recommend initiation of lifelong ART for individuals with CD4 cell counts ≤500 cells/mm^3.[10, 12-15] For adults with CD4 counts >500 cell/mm^3, observational data are less conclusive regarding the potential survival benefit of early treatment.[12, 13, 16] The recommendation for initiation of therapy at CD4 counts >500/mm^3 (BIII evidence) in adults is based on accumulating data that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, the availability of more effective ART regimens with improved tolerability, and evidence that effective ART reduces sexual HIV transmission. However, the Adult Guidelines Panel acknowledges that the amount of data supporting earlier initiation of therapy decreases as the CD4 cell count increases above 500 cells/mm^3, and that concerns remain over the unknown overall benefit, long-term risks, cumulative additional costs, and potential for decreased medication adherence associated with earlier treatment in asymptomatic patients.[10]

Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive HIV-Infected Infants and Children

Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) **(AI*)**.
- ART should be initiated in HIV-infected infants <12 months of age regardless of clinical status, CD4 percentage or viral load (**AI** for infants <12 weeks of age and **AII** for infants ≥12 weeks to 12 months).
- ART should be initiated in HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
    - Age 1 to <3 years
        - with CD4 T lymphocyte (CD4 cell) count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**
    - Age 3 to <5 years
        - with CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**
    - Age ≥5 years
        - with CD4 cell count <350 cells/mm^3 **(AI*)**
        - with CD4 cell count 350–500 cells/mm^3 **(BII*)**
- ART should be considered for HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
    - Age 1 to <3 years
        - with CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
    - Age 3 to <5 years
        - with CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
    - Age ≥5 years
        - with CD4 cell count >500 cells/mm^3 **(BIII)**
- In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment **(BII)**.
- Issues associated with adherence should be assessed and discussed with an HIV-infected child's caregivers before initiation of therapy **(AIII)**. Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Infants Younger than 12 Months of Age

The Children with HIV Early Antiretroviral Therapy (CHER) Trial, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug, antiretroviral therapy (ART) before age 12 weeks in

asymptomatic perinatally infected infants with normal CD4 percentage (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria.[17] Most of the deaths in the infants in the delayed treatment 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 in young infants from the CHER study, the Panel recommends initiating therapy for all infants age <12 months regardless of clinical status, CD4 percentage, or viral load (Table 7). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with an HIV-infected infant's caregivers. However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants <12 months of age.

The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in older infected infants; by age 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[18] In the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given level of CD4 percentage, particularly for infants <12 months of age.[19] 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 (OIs) can occur in young infants with normal CD4 cellcounts.[19]

Identification of HIV infection during the first few months of life permits clinicians to initiate ART 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 start therapy later.[2, 20-23] 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.[24, 25] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. Therapy is not curative, however, as proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued.[26, 27]

However, virologic suppression may take longer to achieve in young children than in older children or adults.[28, 29] Possible reasons for the poor response in infants include higher virologic set points in young infants, inadequate antiretroviral (ARV) drug levels, and poor adherence because of the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70% to 80% have been reported in HIV-infected infants initiating therapy at <12 months of age.[2, 30, 31] In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at <6 months of age, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.[2]

Information on appropriate drug dosing in infants younger than 3 to 6 months is limited. Hepatic and renal functions are immature in newborns undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children.[32] When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. Frequent follow-up and continued assessment and support of adherence are especially important when treating 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.[33] A clinical trial in South Africa is assessing whether it may be possible to stop therapy begun in infancy after a defined duration of treatment that protects a child during the period of greatest risk of HIV disease progression and mortality (such as 1 to 2 years) and then restart therapy when a child meets standard age-related criteria.

Children 1 Year of Age and Older

Disease progression is less rapid in children aged ≥1 year.[18] Children with clinical AIDS or significant symptoms (Clinical Category C or B—Table 6)[34] are at high risk of disease progression and death. The Panel recommends treatment for all such children, regardless of immunologic or virologic status. However, children aged ≥1 year who have mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than children with more severe clinical symptoms.[35] It should also be noted that some Clinical Category B conditions, such as a single episode of serious bacterial infection, may be less prognostic of the risk of disease progression. Consideration of CD4 cell count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, the strength of recommendations to initiate ART in asymptomatic individuals is based primarily on risk of disease progression, as determined by baseline CD4 cell count.[10] In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 cell counts <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 cell counts fell to <350 cells/mm^3, compared with deferring treatment until CD4 cell counts fell to <200 cells/mm^3.[11] 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 adults who started treatment with CD4 cell counts of 200 to 350 cells/mm^3 compared with those who started therapy at CD4 cell counts <200 cells/mm^3.[36]

No randomized trial data exist 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 North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)—suggest a higher rate of progression to AIDS or death in patients deferring treatment until CD4 count is <350 cells/mm^3 compared with patients starting ART at CD4 cell counts of 351 to 500 cells/mm^3.[12, 13] The NA-ACCORD study demonstrated a benefit of starting treatment at CD4 cell counts >500 cell/mm^3 compared with starting ART at CD4 cell counts below this threshold;[12] however the ART-CC cohort found no additional benefit for patients starting ART with CD4 cell counts >450 cells/mm^3.[13] In a third observational study of 5,162 patients with CD4 cell counts between 500 to 799 cells/mm^3, patients who started ART immediately did not experience a significant reduction in progression to AIDS or death (HR: 1.10, 95% CI: 0.67 to 1.79) or death alone (HR: 1.02, 95% CI: 0.49 to 2.12), compared with those who deferred therapy.[15] There are no similar observational data analyses for HIV-infected children.

In children, the prognostic significance of a specific CD4 percentage or count varies with age.[19, 37] In data from the HIV Paediatric 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 in children aged 1 to 4 years than in children aged ≥5 years (Tables 3–4 and Figures 1–2). Data from the HIV Paediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children age ≥5 years, with risk of progression similar to that observed in adults (Table 4).[19, 38] 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).

Because the CD4 percentage is more consistent than the naturally declining CD4 cell count in the first years of life, it has been used preferentially to monitor immunologic status in children <5 years of age. However,

an analysis of >21,000 pairs of CD4 measurements from 3,345 children <1 to 16 years of age in the HIV Paediatric Prognostic Markers Collaborative Study found that CD4 cell counts and percentages were frequently discordant around established World Health Organization (WHO) and the Pediatric European Network for Treatment of AIDS (PENTA) thresholds for initiation of ART (14% and 21%, respectively).[39] Furthermore, CD4 cell counts were found to provide greater prognostic value over CD4 percentage for short-term disease progression for children <5 years as well as in older children. For example, the estimated hazard ratio for AIDS or death at the 10th centile of CD4 cell count (compared with the 50th centile) was 2.2 (95% confidence interval [CI]) 1.4, 3.0) for children 1 to 2 years of age versus 1.2 (CI 0.8, 1.6) for CD4 percentage. Therefore, the updated pediatric guidelines include CD4 cell count thresholds (which differ for children aged 1 to <3, 3 to 5, and ≥5 years due to age-related changes in absolute CD4 cell count) as well as CD4 percentage thresholds for all children >12 months of age. In the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.

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.[37] Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[40-42] and lower neurocognitive performance;[43] similar findings have been reported in adults.[44-46] Similarly, in the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children aged >1 year when HIV RNA levels were ≥100,000 copies/mL (Table 3 and Figures 4–5).[37] For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8 to 10 times higher with plasma HIV RNA >1,000,000 copies/mL.

As with data in adults, data from pediatric studies suggest that improvement in immunologic parameters is better in children when treatment is initiated at higher CD4 percentage/count levels.[29, 47-51] In a study of 1,236 perinatally infected children in the United States, only 36% of those who started treatment with CD4 percentage <15% and 59% of those starting with CD4 percentage 15% to 24% achieved CD4 percentage >25% after 5 years of therapy.[52] Younger age at initiation of therapy has also been associated with improved immune response and with more rapid growth reconstitution.[47, 52, 53] Given that disease progression in children aged ≥5 years is similar to that in adults,[38] and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is <500 cells/mm^3,[12, 13] most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. However, there are no pediatric data to address the optimal CD4 cell count threshold for initiation of therapy in older children; research studies are needed to answer this question in children more definitively. The HHS Adult Treatment Guidelines Committee has moved to endorse initiating ART in all HIV-infected adults regardless of CD4 cell count, using varying strengths of evidence to support different CD4 cell count thresholds[10] and incorporating compelling data demonstrating that ART is effective in preventing secondary transmission of HIV. However, prevention of sexual transmission of HIV is not a significant consideration for children <13 years of age. Comparative studies on the impact of treatment versus treatment delay at specific higher CD4 cell counts have not been performed in children, and observational adult studies have produced conflicting results.[12, 13, 16] Drug choices are more limited in children than in adults and adequate data to address the potential long-term toxicities of prolonged ART in a developing child are not yet available. Some studies have shown that a small proportion of perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by 10 years of age despite receiving no ART.[54-56] Medication adherence is the core requirement for successful virologic control, but enforcing consistent adherence in childhood is often challenging.[57] Incomplete adherence leads to the selection of viral resistance mutations but forced administration of ARVs to children may result in treatment aversion or fatigue, which occurs among many perinatally infected children during adolescence.[58] The relative benefits of initiating ART in asymptomatic children with low viral burdens and high CD4 cell counts must be weighed against these potential risks.

The Panel recommends that ART should be initiated in all children who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [Table 6]), regardless of CD4 percentage/count or HIV RNA level.

The Panel also generally recommends treatment for all children aged ≥1 year with no or mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection [Table 6]), with the strength of recommendation differing based on age and CD4 count/percentage. Patients/caregivers may choose to postpone therapy, and, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

Treatment is strongly recommended regardless of HIV RNA level for children aged 1 to <3 years with CD4 cell counts <1000/mm^3 OR percentage <25%, and for children 3 to <5 years with CD4 cell counts <750 cells/mm^3 OR percentage <25%, based on observational pediatric data.[19] Treatment can also be considered for children aged 1 to <3 years with CD4 cell counts ≥1000/mm^3 and percentage ≥25% and for children 3 to <5 years with CD4 cell counts ≥750 cells/mm^3 and percentage ≥25%, although the strength of the recommendation is lower because of limited data. In these children, plasma HIV RNA levels may be helpful in decision making; plasma HIV RNA >100,000 copies/mL provides higher-rated evidence for treatment, based on pediatric observational data that demonstrate higher mortality risk with high HIV RNA levels.[19, 59]

For children age ≥5 years with no or minimal symptoms, treatment is recommended if CD4 cell counts are ≤500 cells/mm^3, regardless of HIV RNA level. The evidence for this recommendation is strongest for children with CD4 cell counts <350 cells/mm^3. For children with CD4 cell counts 350–500 cells/mm^3, the recommendation is based on observational data in adults and hence the evidence base is not as strong; this recommendation should not prohibit research studies in children designed to answer this question more definitively. Treatment should also be considered for children who are asymptomatic or have mild symptoms with CD4 counts >500 cells/mm^3, although the strength of the recommendation is lower because of limited data. Plasma HIV RNA levels may be helpful in decision making, with plasma HIV RNA >100,000 copies/mL providing higher rated evidence for treatment as noted above.[19, 59]

In general, except in infants and children with advanced HIV infection, ART does not need to be started immediately. Before initiating therapy, it is important to take time to educate caregivers (and older children) about regimen adherence and to anticipate and resolve any barriers that might diminish adherence. This is particularly true for children aged ≥5 years given their lower risk of disease progression and the higher CD4 cell count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor a child's 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 (such as HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for treatment;
- 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

Table 7 provides general guidance rather than absolute recommendations for individual patients. Factors to be considered in decisions about initiation of therapy include 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. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with a child (if age appropriate) and the caregiver. Patients/caregivers may choose to postpone therapy, and, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.[a]

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (**AI** for <12 weeks of age; **AII** for ≥12 weeks)*
1 to <3 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <1000 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count ≥1000 cells/mm^3 or percentage ≥25%	*Treat **(AI*)*** *Treat **(AII)*** *Consider Treatment*[d] ***(BIII)***
3 to <5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <750 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count ≥750 cells/mm^3 or percentage ≥25%	*Treat **(AI*)*** *Treat **(AII)*** *Consider Treatment*[d] ***(BIII)***
≥5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count ≤500 cells/mm^3,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count >500 cells/mm^3	*Treat **(AI*)*** *Treat (**AI*** *for CD4 cell count <350 cells/mm^3 and **BII*** for CD4 cell count 350–500 cells/mm^3)* *Consider Treatment*[d] ***(BIII)***

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

[a] Children in whom ART is deferred need close follow-up. Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:
- Increasing HIV RNA levels (such as HIV RNA levels approaching 100,000 copies/mL);
- CD4 cell count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

[b] CDC Clinical Categories C and B (except for the following Category B condition: single episode of serious bacterial infection)

[c] CDC Clinical Category A or N or the following Category B condition: single episode of serious bacterial infection

[d] The rating of the evidence is stronger for treatment in this group of patients if plasma HIV RNA level is >100,000 copies/mL (BII)

[e] Laboratory data should be confirmed with a second test to meet the treatment criteria before initiation of ART.

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What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children (Last updated November 1, 2012; last reviewed November 1, 2012)

General Considerations

Panel's Recommendations
• Combination therapy consisting of a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor is recommended for initial treatment of HIV-infected children **(AI)**. • The goal of therapy in treatment-naive children is to reduce plasma HIV RNA levels to below the limits of quantitation using the most sensitive assays and to preserve or normalize immune status **(AI)**. • Antiretroviral (ARV) drugs initiated for chemoprophylaxis of maternal-child transmission of HIV should be discontinued in infants who are confirmed to be HIV-infected **(AI)**. • ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants, children, and adolescents (**AII** infants; **AIII** children and adolescents).
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion* *† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents*

More than 20 antiretroviral (ARV) drugs are Food and Drug Administration-approved for use in HIV-infected adults and adolescents and 19 have an approved pediatric treatment indication.[1] The majority of the agents approved for use in pediatric patients are available as a liquid, powder, chewable tablet, or small capsule or tablet suitable for pediatric use. ARV drugs fall into several major drug classes: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in Appendix A: Pediatric Antiretroviral Drug Information. Over time, new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will likely become available, which will increase treatment options for children.

Combination antiretroviral therapy (cART) with at least three drugs from at least two drug classes is recommended for initial treatment of HIV-infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression.[2-5] The goal of cART is to maximally suppress viral replication, preferably to below the limits of quantification, 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 viral mutations that confer resistance to the drugs being used.[4-6]

If an infant is confirmed to be HIV-infected while receiving chemoprophylaxis to prevent mother-to-child transmission (PMTCT) of HIV, prophylactic ARV drugs should be discontinued promptly and treatment initiated with a combination regimen of at least three drugs. Zidovudine can be included as a component of the treatment regimen if zidovudine drug resistance is not detected.

Treatment-naive infants and children with perinatal HIV infection can have drug-resistant virus either because it was transmitted perinatally or during breastfeeding or because resistance developed while they were receiving ARV prophylaxis. Thus, ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants and children. In infants receiving prophylactic ARV drugs for PMTCT, ARV drug resistance testing can be performed at the same time as confirmatory HIV testing or when prophylactic ARV drugs are discontinued. 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 in 19% of 42 infants born from 2000 to 2001.[7, 8] Detection of resistance in the infants was not significantly associated with a history of maternal and infant ARV prophylaxis. Similarly, following initiation of treatment, mutations associated with drug-resistance were detected in 24% of 21 infants at a median age of 9.7 weeks. Most of the mutations were not associated with maternal/infant prophylaxis regimens and resistant virus was persistently archived in the resting CD4 cell reservoir in all the infants. In a study in Africa, infants, regardless of whether they were exposed to nevirapine as part of PMTCT, had higher rates of virologic failure on nevirapine-based regimens compared with lopinavir/ritonavir-based regimens.[9-11] In a Spanish cohort of children, resistance mutations were detected in 13% of treatment-naive children.[12] In the United States and Europe, drug-resistant virus has been identified in 6% to 16% of ARV-naive adults and 18% of adolescents with recently acquired HIV infection.[13-17] For ARV-naive children beyond infancy, limited available data do not demonstrate that resistance testing before initiation of therapy correlates with greater success of initial ART.[18] Nevertheless, because the prevalence of resistance in HIV-infected children is sufficiently high and on the basis of expert opinion, the Panel recommends ARV drug-resistance testing with a genotypic assay before initiation of therapy in all treatment-naive infants and children and use of resistance testing results to select the initial drug combination.[19] (See Antiretroviral Drug-Resistance Testing.) Resistance testing in HIV-infected adolescents and adults is also recommended at entry into care.

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Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Table 8) (Last updated November 15, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- The Panel recommends initiating combination antiretroviral therapy in treatment-naive children using one of the following agents plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone combination (in alphabetical order):
    - For children aged ≥6 years: atazanavir/ritonavir **(AI*)**
    - For children aged ≥3 years: efavirenz **(AI*)**
    - For children aged ≥42 weeks postmenstrual and ≥14 days postnatal: lopinavir/ritonavir **(AI)**
- The Panel recommends the following preferred dual-NRTI backbone combinations (in alphabetical order):
    - For children aged ≥3 months: abacavir + (lamivudine or emtricitabine) **(AI)**
        - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 **(AII*)**.
    - For adolescents, Tanner Stage 4 or 5: tenofovir + (lamivudine or emtricitabine) **(AI*)**
    - For children of any age: zidovudine + (lamivudine or emtricitabine) **(AI*)**
- Table 8 provides a list of Panel-recommended alternative and acceptable regimens.
- Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.
- Alternative regimens may be preferable for some patients based on their individual characteristics and needs.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Criteria Used for Recommendations

In general, Panel recommendations are based on review of pediatric and adult clinical trial data published peer-reviewed journals (the Panel may also review data prepared by manufacturers for Food and Drug Administration review and data presented in abstract format at major scientific meetings). Few randomized, Phase III clinical trials of combination antiretroviral therapy (cART) in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and non-randomized, open-label studies. In general, even in studies in adults, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4 cell) count and HIV RNA levels. The Panel continually modifies recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

Information considered by the Panel for recommending specific drugs or regimens includes:

- 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 (such as powders), volume of syrups, and pill size and number of pills;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies drugs or drug combinations into one of several categories as follows:

- ***Preferred:*** Drugs or drug combinations are designated as *preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies demonstrate that safety and efficacy are suggested using surrogate markers; 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:*** Some drugs and drug combinations are not recommended for initial therapy in children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism. These drugs and drug combinations are listed in Table 9.
- ***Insufficient Data to Recommend:*** For a number of drugs and drug combinations approved for use in adults, PK or safety data in children are unavailable or too limited to make a recommendation on use of the drugs as initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in management of treatment-experienced children, even though they are not recommended for initial therapy in children (see Management of Treatment-Experienced Infants, Children, and Adolescents).

Factors to Consider When Selecting an Initial Regimen

Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Tables 10-14. In addition, because cART will need to be administered lifelong, considerations related to the choice of initial antiretroviral (ARV) 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. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.[1, 2]

Choice of NNRTI- Versus PI-Based Initial Regimens

Preferred regimens for initial therapy include both non-nucleoside reverse transcriptase inhibitor (NNRTI)- and protease inhibitor (PI)-based regimens. The selection of an NNRTI- or PI-based regimen should be based on patient characteristics and preferences, results of viral drug resistance testing, and information cited below.

Recent clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. P1060 compared a nevirapine-based regimen to a lopinavir-based regimen in HIV-infected infants and children aged 2 to 35 months in 7 African countries. Infants and children in this study were stratified at entry based on either prior maternal or infant exposure to single-dose nevirapine prophylaxis for prevention of mother-to-child transmission (PMTCT) and randomized to receive either zidovudine, lamivudine, and nevirapine or zidovudine, lamivudine, and lopinavir/ritonavir. Among infants and children with prior exposure to nevirapine, 39.6% of children in the nevirapine group reached a study endpoint of death, virologic failure, or toxicity by Week 24 compared with 21.7% of children in the lopinavir/ritonavir group.[3] Among infants and children with no prior nevirapine exposure, 40.1% of children treated with nevirapine met a study endpoint after 24 weeks in the study compared with 18.4% of children who received lopinavir/ritonavir.[4] Additional nonrandomized studies have also indicated that infants exposed to nevirapine in the peripartum period as part of PMTCT strategy had a higher risk of treatment failure because of nevirapine resistance.[5-7]

A comparison of a PI-based regimen and a NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children aged 30 days to <18 years in PENPACT-1 (PENTA 9/PACTG 390) (the study did not dictate the specific NNRTI or PI initiated). In the PI-based group, 49% of children received lopinavir/ritonavir and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. Efavirenz was recommended only for children aged >3 years. After 4 years, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial cART regimen. In both groups, 82% of children had viral loads <400 copies/mL, suggesting that selection of an NNRTI or a PI did not influence outcome. Although the age of participants overlapped somewhat between P1060 and PENPACT-1 (in PENPACT-1, the lowest quartile was aged <2.8 years), PENPACT-1 generally enrolled older children.[8]

Results of the P1060 study support the recommendation that a PI-based regimen containing lopinavir/ritonavir should be the preferred initial regimen for children aged <3 years based on superior virologic suppression. However, in both single-dose nevirapine-exposed and -unexposed children in the P1060 study, participants receiving the nevirapine-based regimen demonstrated better immunologic response and growth than those receiving a lopinavir/ritonavir-based regimen, although these differences did not achieve statistical significance. Similarly, in the NEVEREST study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a lopinavir/ritonavir regimen.[9] Based on these findings, the potential for improved lipid profiles with nevirapine use,[9, 10] and the poor palatability of liquid lopinavir/ritonavir, liquid nevirapine remains an acceptable alternative for infants who were not exposed to single-dose nevirapine for PMTCT and who cannot tolerate lopinavir/ritonavir.

In children aged ≥3 years, either an NNRTI-based or a PI-based regimen is acceptable.

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

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an FDA-approved pediatric indication. In the United States, nevirapine is available in a liquid formulation but efavirenz is not. 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

confers lower risk of dyslipidemia and fat maldistribution than use of some agents in the PI class. In addition, for children taking solid formulations, NNRTI-based regimens generally have a lower pill burden than PI-based regimens. The major disadvantages of the current NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance, and cross resistance develops between nevirapine and efavirenz.

In infants, regardless of whether nevirapine is used as part of PMTCT, nevirapine-based regimens demonstrate higher rates of virologic failure than with lopinavir/ritonavir-based regimens.[3, 4] Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all NNRTI drugs, but is most frequent with nevirapine, at least in HIV-infected adults. Like PIs, NNRTIs have the potential to interact with other drugs also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted PI regimens.

Efavirenz, in combination with 2 NRTIs, is the preferred NNRTI for initial therapy of children aged ≥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 (HSRs), including Stevens-Johnson syndrome and rare but potentially life-threatening hepatitis,[11, 12] nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of ARV-naive children.

Etravirine is an NNRTI approved by the FDA for treatment of HIV-1 infection in treatment-experienced patients aged ≥6 years. Rilpivirine, also an NNRTI, is FDA-approved for treatment of HIV-1 infection in treatment-naive adults only. At this time, there is insufficient information to consider either of these agents as initial therapy in children.

Preferred NNRTI

Efavirenz as preferred NNRTI (AI*): 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; 70% of treated adults had plasma HIV RNA <400 copies/mL at 48 weeks.[13] In randomized controlled trials in treatment-naive adults, efavirenz-treated patients had superior or similar virologic activity compared with those receiving PI- or triple NRTI-based regimens.[14-19] Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below).[20-24] In PENPACT-1, subjects receiving efavirenz or nevirapine showed comparable virologic suppression after 4 years.[8] An analysis of children and adults starting first-line cART in Uganda demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years).[25] Few had received nevirapine as part of a PMTCT regimen. In addition, a recent report of 761 children aged 3 to 16 years who received either efavirenz (n = 398) or nevirapine (n = 363) in the Botswana national treatment program demonstrated increased rates of virologic failure among those receiving nevirapine (OR = 2.2, 95% CI 1.5–3.4). Time to virologic failure also favored an efavirenz regimen.[26]

Efavirenz in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) or with an NRTI and a PI has been studied in HIV-infected children.[27-33] Results are comparable to those seen in adults. The appropriate dose of efavirenz for children aged <3 years has not been determined; therefore, efavirenz is not recommended for children in this age group. For children aged ≥3 years, who are unable to swallow pills, some clinicians recommend breaking open efavirenz capsules and adding the contents to food or liquid. Bioequivalence data based on bioavailability and PK support this option.[34]

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults;

reported adverse 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 initiating efavirenz. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the occurrence was more frequent in adults with higher levels of drug.[35-38] 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.[31, 33] In addition, first-trimester exposure to efavirenz is potentially teratogenic (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Although emerging information about the use of efavirenz in pregnancy is reassuring,[39] alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.

Alternative NNRTI

Nevirapine as alternative NNRTI (AI): Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[40] Nevirapine in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children.[41-43]

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).[24] In the ARTEN trial, antiretroviral therapy-naive participants were randomized to nevirapine 200 mg twice daily, nevirapine 400 mg once daily, or ritonavir-boosted atazanavir, all in combination with tenofovir disoproxil fumarate (tenofovir)/emtricitabine. By 48 weeks, similar proportions of subjects in each group had at least 2 consecutive plasma HIV RNA levels <50 copies/mL (66.8% for nevirapine vs. 65.3% for ritonavir-boosted atazanavir) but more participants in the nevirapine arms discontinued study drugs because of adverse events (13.6% vs. 2.6%, respectively) or lack of efficacy (8.4% vs. 1.6%, respectively).[44]

Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens.[45] In addition, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 T lymphocyte (CD4 cell) counts and in women, particularly women with CD4 cell counts >250 cells/mm^3 and men with CD4 cell counts >400 cells/mm^3. A more recent study including 820 women in Kenya, Zambia, and Thailand demonstrated that hepatic toxicity was associated with elevated baseline liver function tests and not CD4 cell count at the time of nevirapine initiation.[46] In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults.[42, 43, 47] 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 child; there was no evidence of a serious hepatic event associated with nevirapine use in any child before adolescence.[47] A recent report of 1,434 children in Malawi receiving treatment with a nevirapine-based regimen noted that only 0.14% of the children discontinued the regimen because of hepatic toxicity.[48] In contrast, skin reactions and HSRs associated with nevirapine use have been reported in children.[49] However, it should be noted that data are limited about the relationship between CD4 cell count and percentage in children at the time they initiate nevirapine and the development of toxicity. In a study of 201 HIV-infected children in Asia initiating cART (137 randomized to a nevirapine-containing regimen), the development of overall toxicities, including rash and hepatotoxicity, was almost three-fold higher in children initiating cART when CD4 percentage was ≥15%.[50] 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 this substitution should be attempted with caution.[51]

Because of the greater potential for toxicity and possibly increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children aged ≥3 years. In children aged <3 years, nevirapine is considered an alternative because of increased risk of virologic failure. Even if not exposed to nevirapine as part of PMTCT, infants on nevirapine-based regimens had higher rates of virologic failure than infants on lopinavir/ritonavir-based regimens.[3-5, 52] However, infants treated with nevirapine showed a trend toward greater improvement in both immunologic status and growth.[3]

A recent study randomized infants exposed to nevirapine who had achieved viral suppression for an average of 9 months using lopinavir/ritonavir-based therapy as part of a PMTCT regimen to continuation of the lopinavir/ritonavir regimens or a switch to a nevirapine-based regimen. After 52 weeks of follow up, plasma viremia ≥50 copies/mL occurred less frequently in the switched group compared with the continuation group. CD4 response was also better in the switched group. However, 20% of the switched group experienced breakthrough viremia (confirmed viral load >1,000 copies/mL) and subsequent analysis demonstrated that failure was associated with higher (>25%) frequencies of pretreatment NNRTI mutations.[53] These findings suggest this strategy may be an option for children in whom standard genotyping before treatment detects no NNRTI mutations but should be undertaken with careful monitoring of viral load.[9]

Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4 cell counts >250/mm^3 because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk.[12] Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

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

Summary: PI-Based Regimens

Nine PIs are currently FDA-approved for use and 7 are approved for use in children. 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, because PIs are metabolized via hepatic enzymes the drugs have potential for multiple drug interactions. They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider in selecting a PI-based regimen for treatment-naive 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. (Table 12 lists the advantages and disadvantages of PIs. See Appendix A: 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 coadministered with ritonavir. The drug has been used in low doses combined with another PI as a PK booster, increasing drug exposure by prolonging the half-life of the second, boosted PI. Boosted PI-based regimens are commonly used in treatment of adults and pediatric data are available for several combinations. Co-formulated lopinavir/ritonavir has been studied in infants as young as age 25 days[54] and is FDA-approved for use in infants after a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days. Fosamprenavir with low-dose ritonavir is FDA-approved in infants and children aged ≥4 weeks, although the Panel only recommends use in those aged 6 months and older. Darunavir with low-dose ritonavir is FDA-approved in children aged ≥3 years and atazanavir and tipranavir with low-dose ritonavir are FDA-approved in children aged ≥6 years. In addition, the use of low-dose ritonavir increases the potential for hyperlipidemia[55] and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated lopinavir/ritonavir as the preferred PI for initial therapy in children 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, and experience as initial therapy in both resource-rich and resource-limited areas. Although lopinavir/ritonavir can be used in children aged ≥42 weeks postmenstrual and aged ≥14 days postnatal, at the current time, atazanavir with low-dose ritonavir should be used only in children aged ≥6 years. Two additional PIs—fosamprenavir and darunavir—can be considered as alternative PIs for use in children. Fosamprenavir is FDA-approved for treatment of HIV infection in infants aged ≥4 weeks and older. However, because of low drug exposure in infants aged <6 months, the Panel recommends use only in patients aged ≥6 months. Darunavir can also be used for children aged ≥3 years. Both fosamprenavir and darunavir should be used in combination with low-dose ritonavir. 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 aged ≥2 years, atazanavir without boosting ritonavir in adolescents aged ≥13 years and weighing >39 kg, and nelfinavir in children aged ≥2 years. A saquinavir/ritonavir (1000/100 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-naive adults.[56] However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation and dosing and outcome data on saquinavir use in children are limited. Although good virologic and immunologic responses have been observed with indinavir-based regimens in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis in pediatric patients using indinavir have been reported.[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 in children. Tipranavir currently is not recommended for initial therapy in treatment-naive children because experience with the drug is limited.

Preferred PIs

Atazanavir with low-dose ritonavir as preferred PI (for children ≥6 years) (AI*): Atazanavir is a once-daily PI that was FDA-approved in March 2008 for use in children aged ≥6 years. It has efficacy equivalent to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naive adults.[18, 61-63] Seventy-three percent of 48 treatment-naive 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.[64] Among 43 treatment-naive children aged 6 to18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 51% and 47% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 96 weeks.[65, 66] When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children aged ≥6 years[67-69] and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting.[70] 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 with low-dose ritonavir boosting than with atazanavir alone.[55]

Lopinavir/ritonavir as preferred PI (for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days) (AI): In clinical trials in adults, regimens containing lopinavir/ritonavir plus 2 NRTIs have been found to have potent virologic activity in treatment-naive patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had virologic efficacy superior 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.[71, 72] The groups had similar rates of toxicity. Lopinavir/ritonavir has been studied in both ARV-naive and -experienced children and has demonstrated durable virologic activity and low toxicity (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[3, 73-80] In addition, dosing and efficacy data in infants as young as 25 days of age are available.[54, 77] Post-marketing reports of lopinavir/ritonavir-associated cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in lopinavir/ritonavir labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. In addition, although once-daily lopinavir/ritonavir is FDA-approved for initial therapy in adults,[81] PK data in children do not support a recommendation for once-daily dosing in children.[82, 83]

Alternative PIs

Darunavir with low-dose ritonavir as alternative PI (for children aged ≥3 years) (AI*): Darunavir combined with low-dose ritonavir is FDA-approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children aged ≥3 years. In a randomized, open-label trial in adults, darunavir/ritonavir (800/100 mg once daily) was found to be non-inferior to lopinavir/ritonavir (once or twice daily), when both boosted PIs were administered in combination with tenofovir/emtricitabine. Plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and 78% of lopinavir/ritonavir recipients at 48 weeks and 79% of darunavir/ritonavir recipients and 71% of lopinavir/ritonavir recipients at 96 weeks (P <0.001, for each comparison). Adverse events were also less common in the darunavir/ritonavir group (P <0.01).[84, 85] In a study of treatment-experienced children (aged 6–17 years), twice-daily darunavir/ritonavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.[86] In another study of treatment-experienced pediatric subjects (aged 3–<6 years and weight ≥10 kg–<20 kg), 57% of subjects had HIV-1 RNA less than 50 copies/mL and 81% were less than 400 copies/mL after 24 weeks of treatment.[87] Twenty children completed the trial; one stopped prematurely because of vomiting. Once-daily darunavir/ritonavir has been studied in treatment-naive adolescents aged 12 to 18 years (mean age, 14.6 years). After 24 weeks of treatment, 11 of 12 subjects had HIV-1 RNA <50 copies/mL.[88] Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from these studies 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. While twice-daily dosing of darunavir with ritonavir boosting is recommended as an alternative PI for children aged ≥3 years, once-daily dosing of darunavir currently should only be considered for treatment-naive adolescents aged >12 years.

Fosamprenavir with low-dose ritonavir as alternative PI (for children aged ≥6 months) (AI*): 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 FDA-approved for use in pediatric patients aged ≥2 years. The approval was based on two open-label studies in pediatric patients aged 2 to 18 years.[89, 90] In 2012, fosamprenavir was FDA-approved for use in PI-naive children as young as 4 weeks who were born at ≥38 weeks' gestation and had attained a postnatal age of 28 days. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see Appendix A: 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.[91] In children aged ≥4 weeks, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. In addition, because of low drug exposure, the Panel recommends fosamprenavir with low-dose ritonavir only for children aged ≥6 months. 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 (BII*): Although unboosted atazanavir is FDA-approved for treatment-naive adolescents aged ≥13 years who weigh >39 kg and are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m^2 basis) are required in adolescents than in adults to achieve adequate drug concentrations[69] (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naive patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because this combination demonstrated inferior virologic response in adults in ACTG 5175.[92] If didanosine, emtricitabine, **and** atazanavir are used in combination, patients should be instructed to take didanosine and atazanavir at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach.

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

Nelfinavir for children aged ≥2 years (BI*): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children aged ≥2 years in special circumstances. The pediatric experience with nelfinavir-based regimens in ARV-naive and -experienced children is extensive, with follow-up in children receiving the regimen for as long as 7 years.[93] The drug has been well tolerated—diarrhea is the primary adverse effect; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression ranging from 26% to 69% (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients.[94] 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% of children with therapeutic nelfinavir troughs (>0.8 mg/L).[94] The interpatient variability in plasma concentrations is great in children, with lower levels in younger children.[95-100] The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. These data, combined with data in adults showing inferior potency of nelfinavir compared with other PIs and efavirenz, balanced against the advantage of a PI that is not coadministered with low-dose ritonavir for boosting,[72, 101-104] make nelfinavir an agent for use in special circumstances in treatment-naive children aged ≥2 years and not recommended for treatment of children aged <2 years.

Nelfinavir is currently available only as tablets, which can be 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 PK parameters in a study in adults.[105]

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

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, seven NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and tenofovir) are FDA-approved for use in children <13 years of age. Tenofovir is FDA-approved for use in children and adolescents aged ≥2 years. Because of decreases in bone mineral density (BMD) observed in adults and children receiving tenofovir, the Panel has opted to consider use of tenofovir based on Tanner stage and only in children aged ≥2 years. We have reserved our strongest recommendation for adolescents who are in the late stages of or who have completed puberty (Tanner stages 4 and 5). Tenofovir can be used in younger children after weighing potential risks of decreased BMD versus benefits of therapy. It is important to note that although decreases in BMD are observed, the clinical significance of these changes is not yet known. 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; emtricitabine in combination with stavudine or didanosine; and tenofovir in combination with lamivudine or emtricitabine.[1, 29, 67, 93, 99, 106, 107, 114-119] Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 10.

Preferred Dual-NRTI Regimens

The dual-NRTI combinations preferred for initial therapy in children are abacavir or zidovudine combined with either lamivudine or emtricitabine, and in adolescents who are Tanner Stage 4 or 5, tenofovir combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine **(AI*)**. Data on the safety of this combination in children are extensive and the combination is generally well tolerated. The major toxicity associated with zidovudine/lamivudine is bone marrow suppression, manifested as macrocytic anemia and neutropenia; minor toxicities include gastrointestinal toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few adverse effects. Although there is less experience in children with emtricitabine than with lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (that is, emtricitabine in combination with abacavir or zidovudine). The advantages of emtricitabine are that it can be administered once daily and it is available 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 based on decreased viral fitness.[108, 109]

Abacavir in combination with lamivudine **(AI)** has been shown to be as potent or, possibly, more potent than zidovudine in combination with lamivudine in both children and adults.[110, 111] However, abacavir/lamivudine has the potential for abacavir-associated life-threatening HSRs 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.[111] Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see Appendix A: Pediatric Antiretroviral Drug Information); however, in the United States, the prevalence of HLA-B*5701 is much lower in African Americans and Hispanics (2%–2.5%) than in whites (8%).[112] Pretreatment screening for HLA-B*5701 before initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir HSRs in HIV-infected adults (from 7.8% to 3.4%).[113] Before initiating abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir **(AII*)**.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an oral sprinkle/granule formulation.[114-117] The use of tenofovir in pediatric patients aged 2 to <18 years is approved by the FDA based on data from two randomized studies. In study 321, 87 treatment-experienced subjects aged 12 to <18 years, were randomized to receive tenofovir or placebo plus optimized background regimen (OBR) for 48 weeks. Although there was no difference in virologic response between the two groups, the safety and PKs of tenofovir in children in the study were similar to those in adults receiving tenofovir.[118] In study 352, 92 treatment-experienced children, aged 2 to <18 years with virologic suppression on stavudine- or zidovudine-containing regimens were randomized to either replace stavudine or zidovudine with tenofovir or continue their original regimen. After 48 weeks, 89% of subjects receiving tenofovir and 90% of subjects continuing their original regimen had HIV-1 RNA concentrations <400 copies/mL.[119]

Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents Tanner Stage 4 or 5 **(AI*)**. The fixed-dose combination of tenofovir and emtricitabine and the fixed-dose triple combination of tenofovir, emtricitabine, and efavirenz both allow for once-daily dosing,

which may help 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.[120, 121] In ACTG 5202, adults were randomly assigned to tenofovir/emtricitabine versus abacavir/lamivudine in combination with boosted atazanavir versus efavirenz (in factorial design). Among adults with screening HIV-1 RNA ≥100,000 copies per mL, the time 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.[122] A study of 688 adults receiving lopinavir/ritonavir in addition to the randomized backbone of either tenofovir/emtricitabine or abacavir/lamivudine showed no difference in antiviral efficacy, safety, or tolerability at 48 weeks.[123] In 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-naive adults.[124] Also, no difference in virologic response was demonstrated in a meta-analysis of combination regimens containing tenofovir or zidovudine. However, tenofovir-containing regimens demonstrated better immunologic response, adherence, and less resistance.[125]

In some, but not all, studies, decreases in BMD have been observed in both adults and children taking tenofovir for 48 weeks.[114-117, 126, 127] At this time, data are insufficient to recommend use of tenofovir as part of a preferred regimen for initial therapy in infected children in Tanner Stages 1 through 3, for whom the risk of bone toxicity may be greatest.[114, 117] (See Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information.) Renal toxicity has been reported in children receiving tenofovir.[128-131] Given the potential for bone and renal toxicity, tenofovir may be more useful for treatment of children in whom other ARV drugs have failed than for initial therapy of treatment-naive younger children. Numerous drug-drug interactions with tenofovir and other ARV drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, complicate appropriate dosing of tenofovir.

Alternative Dual-NRTI Regimens

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine **(BII)**, didanosine in combination with lamivudine or emtricitabine **(BI*)** and tenofovir in combination with lamivudine or emtricitabine in children and adolescents who are Tanner Stage 3 (as opposed to Tanner Stages 4 and 5, where this is a preferred dual-NRTI regimen) **(BI*)**. There is considerable experience with use of these dual-NRTI regimens in children, and in a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[132] However, zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in 1 European pediatric study.[99, 111] The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children aged 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.[29] Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who must be fed frequently and it may decrease medication adherence in older children because of the complexity of the regimen. 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.[133] To improve adherence, some practitioners recommend administration of didanosine without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

Dual-NRTI Regimens for Use in Special Circumstances

The dual-NRTI combinations of stavudine with lamivudine or emtricitabine in children of any age are recommended for use in special circumstances. Stavudine is recommended for use only in special circumstances because the ARV is associated with a higher risk of lipoatrophy and hyperlactatemia than

other NRTI drugs.[134-136] Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations.[132] In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferable to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

In children aged ≥2 who are prepubertal or in the early stages of puberty (Tanner Stages 1 and 2), tenofovir in combination with lamivudine or emtricitabine is also recommended for use in special circumstances. As discussed above, the use of tenofovir during puberty when bone toxicity may be greatest may require caution. However, tenofovir may be a reasonable choice for initial therapy in children with demonstrated resistance to other NRTIs, co-infection with hepatitis B virus, or in those desiring a once-daily NRTI where abacavir is not an option. The Panel awaits additional safety data, especially with the recently licensed powder formulation, before providing a broader recommendation in younger children.

Dual-NRTI Regimens Not Recommended

Certain dual-NRTI drug combinations are not recommended. These include zidovudine plus stavudine because of 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 because of potentially greater toxicity. In small pediatric studies, stavudine/didanosine demonstrated virologic efficacy and was well tolerated.[106, 107, 137] However, in studies in adults, stavudine plus didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine plus lamivudine;[138, 139] in addition, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy.[134, 140] 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.

All-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 ARV-naive children are limited; in small observational studies, response rates of 47% to 50% have been reported.[141, 142] 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 plus lamivudine plus 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-naive children (such as because of significant drug interactions or concerns related to adherence) **(BI*)**.

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

Zidovudine + lamivudine + abacavir: The triple-NRTI combination of zidovudine + lamivudine + abacavir has been demonstrated to have virologic efficacy comparable to indinavir-[143] or nelfinavir-containing regimens[144] but was inferior to an efavirenz-based regimen.[14, 145] 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.[146]

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.[147, 148] 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. Tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine demonstrate significantly increased rates of virologic failure and are not recommended.[149-151] The tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults; however, no comparative data are available and the regimen is not recommended.[152]

Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children

Not Recommended for Initial Therapy for Children Because of Insufficient Data

A number of ARV drugs and drug regimens are not recommended for initial therapy of ARV-naive children because of insufficient pediatric data **(AIII)**. 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-naive children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options.[30-32]

Regimens containing three NRTIs and an NNRTI: Data are currently insufficient to recommend a regimen of three NRTIs plus an NNRTI in young infants. A recent review of nine cohorts from 13 European countries contributed data on HIV-infected infants born from 1996 through 2008 who initiated therapy before age 12 months. Superior responses to this four-drug regimen were observed compared to boosted PI or three-drug NRTI regimens.[153] It is speculated that poor tolerance and adherence to a PI-based regimen may account for differences. Based on demonstated benefits of recommended three-drug regimens and lack of additional safety and efficacy data on the four-drug regimen, the Panel currently does not recommend this regimen.

New agents without sufficient pediatric data to recommend use as initial therapy (Tables 13 and 14): At this time several new agents that appear promising for use in adults do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (a CCR5 antagonist), raltegravir and elvitegravir (both integrase inhibitors), and etravirine and rilpivirine (both NNRTIs). Raltegravir is FDA-approved for treatment of HIV-1-infected children aged ≥2 years and weight ≥10 kg. It is available in film-coated tablets and chewable tablets. Oral granules for suspension are currently under investigation. Safety and efficacy data are promising, but at this time, data are insufficient to recommend as initial therapy.[154-156] In June 2008, FDA approved tipranavir boosted with ritonavir for use in treatment-experienced children aged 2 to 18 years; however, data are insufficient to consider use of the agent for initial therapy. Elvitegravir, another integrase inhibitor, is only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, and is FDA-approved for use as a complete ARV regimen in HIV-1-infected ARV treatment-naive adults. It is not FDA-approved for use in children aged <18 years. There are no data on its use in individuals younger than age 18 years, and it cannot be considered for use as initial therapy for children at this time (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf).

Enfuvirtide, a fusion inhibitor, is FDA-approved for use in combination with other ARV drugs to treat children aged ≥6 years who have evidence of HIV replication despite ongoing cART (that is, treatment-experienced children on nonsuppressive regimens). The drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Currently, data are insufficient to recommend use of enfuvirtide for initial therapy of children.

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

Several ARV 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.

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

- *A single ARV drug (monotherapy)* **(AII)**
- *Two NRTIs alone* **(AI)**
- *Certain dual-NRTI combinations as part of a combination regimen:*
  - *Lamivudine + emtricitabine because of similar resistance patterns and no additive benefit* **(AIII)**
  - *Zidovudine + stavudine because of 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*)**

Monotherapy: Therapy with a single ARV drug is not recommended for HIV treatment because monotherapy is unlikely to result in sustained viral suppression, leading to development of viral resistance to the drug used and cross resistance to other drugs in the same drug class. However, use of zidovudine alone is appropriate for prophylaxis for the newborn of an HIV-infected mother. In this setting, 6 weeks of monotherapy with zidovudine is recommended for the infant. In the event the infant is identified as HIV infected, zidovudine should be discontinued and standard triple therapy initiated.[140]

In a child with treatment failure associated with drug resistance and persistent nonadherence, monotherapy using an interim bridging regimen of lamivudine alone can be considered. Bridging regimens have been reported to be effective in delaying immunologic decline in adults with failing combination therapy, often because of to nonadherence.[157, 158] Bridging regimens should not be considered as initial therapy and should only be used in the interim as a clinician works intensively with the patient and caregivers to improve adherence before initiating a new, suppressive cART regimen (see Approach to the Management of Antiretroviral Treatment Failure).

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 development of viral resistance to the drugs being used and cross resistance to other drugs within the same drug class. For children who have achieved viral suppression on a previously initiated dual-NRTI regimen, it is reasonable to either continue on this therapy or to add a PI or a NNRTI to the regimen. However, a child remaining on a dual-NRTI regimen should be switched to a 3-or-more drug combination if viral rebound occurs (see Management of Treatment-Experienced Infants, Children, and Adolescents).

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

Dual NNRTIs: An adult study (2NN) demonstrated increased toxicity with the combination of nevirapine plus efavirenz.[24]

Certain PIs: The combination of atazanavir plus indinavir has the potential for additive hyperbilirubinemia. Unboosted saquinavir, darunavir, and tipranivir have low bioavailablity and do not achieve adequate drug levels; therefore, they 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-naive adults and are not recommended as combination therapy for children at any time.[149-151]

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 1 of 2)

A combination ARV regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Tables 10–14).

Preferred Regimens	
Children aged ≥14 days to <3 years[a]	Two NRTIs ***plus*** LPV/r
Children aged ≥3 years	Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Children aged ≥6 years	Two NRTIs ***plus*** ATV ***plus*** low-dose RTV Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Alternative Regimens	
Children of any age	Two NRTIs ***plus*** NVP[c]
Children aged ≥3 years	Two NRTIs ***plus*** DRV ***plus*** low-dose RTV
Children aged ≥6 months[d]	Two NRTIs ***plus*** FPV ***plus*** low-dose RTV
Regimens for Use in Special Circumstances	
Two NRTIs ***plus*** ATV unboosted (for treatment-naive adolescents aged ≥13 years and weight >39 kg) Two NRTIs ***plus*** FPV unboosted (children aged ≥2 years) Two NRTIs ***plus*** NFV (children aged ≥2 years) Zidovudine ***plus*** 3TC ***plus*** ABC	
2-NRTI Backbone Options for Use in Combination with Additional Drugs (in alphabetical order)	
Preferred	ABC ***plus*** (3TC ***or*** FTC) (children aged ≥3 months) TDF ***plus*** (3TC ***or*** FTC) (adolescents, Tanner Stage 4 or 5) ZDV ***plus*** (3TC ***or*** FTC)
Alternative	ddI ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents,Tanner Stage 3) ZDV ***plus*** ABC ZDV ***plus*** ddI
Use in Special Circumstances	d4T ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (prepubertal children aged ≥2 years and adolescents, Tanner Stage 1 or 2)
Not Recommended for Initial Therapy	
ETR-containing regimens EFV-containing regimens for children aged <3 years TPV-containing regimens SQV-containing regimens	

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

Not Recommended for Initial Therapy
IDV-containing regimens
Dual (full-dose) PI regimens
Full-dose RTV or use of RTV as the sole PI
Unboosted ATV-containing regimens in children aged <13 years and/or weight <39 kg
NFV-containing regimens for children aged <2 years
Unboosted DRV-containing regimens
Once-daily dosing of boosted DRV in children aged <12 years
Once-daily dosing of LPV/r or boosted or unboosted FPV
Triple-NRTI regimens other than ABC + ZDV + 3TC
Triple-class regimens, including NRTI ***plus*** NNRTI ***plus*** PI
Four-drug regimens with three NRTIs ***plus*** NNRTI
Regimens with dual-NRTI backbones of ABC + ddI, ABC + TDF, and ddI + TDF
TDF-containing regimens in children aged <2 years
MVC-containing regimens
RPV-containing regimens
RAL-containing regimens
T-20-containing regimens
EVG-containing regimens

[a] LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

[b] EFV should be used only in children aged ≥3 years with weight ≥10 kg. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

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

[d] FPV with low dose ritonavir should only be administered to infants born at ≥38 weeks gestation who have attained a postnatal age of 28 days and to infants born before 38 weeks gestation who have reached a postmenstrual age of 42 weeks.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, EVG = elvitegravir, FPV = fosamprenavir, FTC = emtricitabine, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide, TDF = tenofovir, RPV = rilpivirine, TPV = tipranavir, ZDV = zidovudine

Table 9. ARV Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children

	Rationale	Exceptions
ARV regimens never recommended for children		
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV • 3TC or FTC interim "bridging regimen" in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy • For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.
TDF ***plus*** ABC ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions
TDF ***plus*** ddI ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions
ARV components never recommended as part of an ARV regimen for children		
ATV ***plus*** IDV	• Potential additive hyperbilirubinemia	• No exceptions
Dual-NNRTI combinations	• Enhanced toxicity	• No exceptions
Dual-NRTI combinations: • 3TC ***plus*** FTC • d4T ***plus*** ZDV	• Similar resistance profile and no additive benefit • Antagonistic effect on HIV	• No exceptions • No exceptions
EFV 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 ARV option is available and potential benefits outweigh risks
NVP in adolescent girls with CD4 count >250 cells/mm^3 or adolescent boys with CD4 count >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs risk
Unboosted SQV, DRV, or TPV	• Poor oral bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, IDV = indinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Preferred Combinations		
ABC ***plus*** (3TC ***or*** FTC)	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
ZDV ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill for older/larger patients. • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 4 or 5	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients.	• Limited pediatric experience • Potential bone and renal toxicity • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.
Alternative Combinations		
ddI ***plus*** (3TC ***or*** FTC)	• Delayed-release capsules of ddI may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily FTC. • FTC available as a palatable liquid formulation administered once daily.	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, neurotoxicity with ddI
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 3	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential for bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Alternative Combinations, continued		
ZDV ***plus*** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. • Bone marrow suppression and lipoatrophy with ZDV
ZDV ***plus*** ddI	• Extensive pediatric experience • Delayed-release capsules of ddI may allow once-daily dosing of ddI in older children able to swallow pills and who can receive adult doses.	• Bone marrow suppression and lipoatrophy with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation. • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue.
Use in Special Circumstances		
d4T ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Limited pediatric experience with d4T plus FTC
TDF ***plus*** (3TC ***or*** FTC) for children, Tanner Stage 1 or 2	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
Not Recommended		
3TC ***plus*** FTC	• None	• Similar drug structure • Single mutation (M184V) associated with resistance to both drugs
d4T ***plus*** ddI	• Has shown antiviral activity in small studies in children • Although not recommended for initial therapy, it can be considered for use in ARV-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
ZDV ***plus*** d4T	• None	• Pharmacologic and antiviral antagonism

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HSR = hypersensitivity reaction, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PK = pharmacokinetic, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
NNRTI-based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than PIs • PI sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens.	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, 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		
EFV (for children aged ≥3 years who can take capsules)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.
Alternative		
NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a PMTCT regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing
Not Recommended		
EFV (for children aged <3 years)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Not Recommended, continued		
ETR	• 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 ETR-related rash.	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naive patients • Multiple drug interactions with PIs and other medications • Twice-daily dosing • Skin rash
RPV	• Once-daily administration • Reduced CNS effects compared with EFV • Not associated with embryofetal abnormalitites	• No data on pediatric dosing or safety • No pediatric formulation available • Compared with EFV, has higher rate of treatment failure and cross resistance to the NNRTI class in adults • Adults with viral loads >100,000 copies/mL are more likely to experience virologic failure than are patients with viral loads <100,000 copies/mL.

Key to Abbreviations: ARV = antiretroviral, CNS = central nervous system, CYP3A4 = cytochrome P450, EFV = efavirenz, ETR = etravirine, HSR = hypersensitivity reaction, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PMTCT = prevention of mother-to-child transmission, SJS = Stevens-Johnson syndrome, RPV= rilpivirine

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
PI-based Regimens	**PI Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to PIs requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**PI Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
ATV in combination with low-dose RTV in children aged ≥6 years	• Once-daily dosing • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG)
LPV/r	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack.	• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone • Food effect (liquid formulation should be administered with food) • RTV component associated with large number of drug interactions (see RTV) • Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Alternative		
DRV in combination with low-dose RTV in children aged ≥3 years	• Effective in PI-experienced children when given with low-dose RTV boosting	• Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. • Cannot administer once daily in children aged <12 years

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
FPV in combination with low-dose RTV in children aged ≥6 months	• Oral prodrug of APV with lower pill burden • Pediatric formulation available, which should be given to children with food	• Skin rash • More limited pediatric experience than preferred PI • Must be given with food to children • RTV component associated with large number of drug interactions (see RTV) • Contains sulfa moiety. Potential for cross sensitivity between FPV and other drugs in sulfonamide class is unknown. • Should only be administered to infants born at ≥38 weeks' gestation and who have attained a postnatal age of 28 days
Use in Special Circumstances		
ATV (unboosted) in treatment-naive adolescents aged ≥13 years and weight >39 kg who are unable to tolerate RTV	• Once-daily dosing • Less effect on TG and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations • Unboosted ATV cannot be used with TDF
FPV (unboosted) in children aged ≥2 years	• Oral prodrug of APV 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; PK data to define appropriate dosing not yet available.
NFV in children aged ≥2 years	• Can give with food • Simplified 2-tablet (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 • 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 than boosted PIs

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 3 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information

	Advantages	Disadvantages
Not Recommended		
ATV (unboosted) in children aged <13 years and/or weight <39 kg	• Once-daily dosing (aged >13 years) • Less effect on TG and total cholesterol levels than other PIs	• Drug levels low if used without RTV boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used in caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations
IDV (unboosted or boosted)	• Can be considered for use as component of a regimen in combination with low-dose RTV 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 RTV • High fluid intake required to prevent nephrolithiasis • Food effect (should be taken 1 hour before or 2 hours after food) • Limited pediatric PK data
NFV in children aged <2 years	• Can give with food	• Diarrhea • 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 than boosted PIs
RTV (full dose as single PI)	• Liquid formulation • Can give with food	• Poor palatability of liquid (bitter taste) • GI intolerance • Food effect (should be administered with food) • Large number of drug interactions (most potent inhibitor of CYP3A4)
SQV (unboosted or boosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric PK data; will require boosting with another PI (e.g., RTV) to achieve adequate concentrations. • No liquid formulation • High pill burden • Must be taken with food • Potential for photosensitivity reactions

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 4 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
TPV	• Effective in PI-experienced children and adults when given with low-dose RTV boosting • Liquid formulation	• Limited data in treatment-naive patients • Food effect (should be administered with food) • Must be given with RTV boosting to achieve adequate plasma concentrations

Key to Abbreviations: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, CYP3A4 = cytochrome P450, DRV = darunavir, ECG = electrocardiogram, FPV = fosamprenavir, GI = gastrointestinal, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TG = triglyceride, TPV = tipranavir

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Combination ARV Regimens (see Pediatric Antiretroviral Drug Information Appendix for more information)

	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 T-20 • CCR5 inhibitors are ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus.
Use in Special Circumstances		
T-20	• 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 because of local site reactions
Insufficient Data to Recommend		
MVC	• 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 NNRTI or PI coadministered with MVC.

Key to Abbreviations: ARV = antiretroviral, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, T-20 = enfuvirtide

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Combination ARV 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		
EVG only available as a coformulated product containing EVG/COBI/FTC/TDF	• One tablet, once daily • The single tablet is a complete combination regimen in antiretroviral-naive patients.	• No data on use in patients aged <18 years • Potential bone and renal toxicity • Potential for many drug interactions from cobicistat (COBI), a CYP3A4 inhibitor with pharmacokinetic actions similar to RTV • Must be taken with food
RAL	• Susceptibility of HIV to a new class of ARVs • Can give with food • Available in a chewable tablet	• Limited data on pediatric dosing or safety • Potential for rare systemic allergic reaction or hepatitis

Key to Abbreviations: ARV = antiretroviral, COBI = cobicistat, EVG = elvitegravir, FTC = emtricitabine, RAL = raltegravir, RTV= ritonavir, TDF = tenofovir disoproxil fumarate

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Monitoring of Children on Antiretroviral Therapy (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Within 1 to 2 weeks after starting a new antiretroviral (ARV) regimen, children should be evaluated to screen for clinical side effects and to ensure patient and caretaker adherence to the regimen **(AIII)**. Evaluations can be conducted in person or over the phone.
- After starting or changing therapy, more frequent evaluation may be needed to support adherence to the regimen **(AIII)**.
- At least every 3 to 4 months thereafter, children should have a monitoring evaluation to assess both effectiveness and potential toxicity of their ARV regimens **(AII*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Children who start antiretroviral therapy (ART) or who change to a new regimen should be followed to assess effectiveness, tolerability, and side effects of the regimen and to evaluate medication adherence. Frequent patient visits and intensive follow-up during the initial months after a new antiretroviral (ARV) regimen is started are necessary to support and educate the family. The first few weeks of ART 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 both children and their caregivers need assistance to determine whether the effects are temporary and can be tolerated or are more serious or long-term and require a visit to the clinician. Thus, it is prudent for clinicians to assess children within 1 to 2 weeks of initiating therapy, either in person or with a phone call, to ensure that medications are being administered properly and evaluate clinical concerns. Many clinicians schedule additional contact (in person or over the telephone) with children and their caregivers during the first few weeks of therapy to support adherence. It is critical that providers speak to caregivers and children in a supportive manner using layman's terms. This promotes honest report(s) and ensures dialogue between providers and both children and their caregiver(s), even when medication adherence is reported to be inconsistent.

Baseline laboratory assessments including CD4 T lymphocyte (CD4 cell) count/percentage and HIV RNA level, complete blood count (CBC) and differential, serum chemistries (including electrolytes, blood urea nitrogen [BUN], creatinine, glucose, hepatic transaminases, calcium, and phosphorus), urinalysis, and serum lipid evaluation (cholesterol, triglycerides) should be done before initiation of therapy. A baseline assessment of ARV resistance using a genotype assay also is recommended (see Antiretroviral Resistance Testing). Within 4 to 8 weeks after initiating or changing therapy, children receiving ART should be seen to obtain a clinical history, with focus on potential adverse effects of ARVs and adherence to medications; to receive a physical examination; and to receive laboratory tests to evaluate the effectiveness of therapy (CD4 count/percentage, plasma HIV RNA level [viral load]) and to detect medication-related toxicities. At a minimum, laboratory assessments should include a CBC and differential, serum chemistries, and assessments of renal and hepatic function. After a change in therapy, more frequent evaluation may be needed to support

adherence to the regimen. Assessment of initial virologic response to therapy is important because an initial decrease in HIV viral load in response to ART should be observed after 4 to 8 weeks of therapy.

Thereafter, medication adherence and regimen toxicity and effectiveness should be assessed every 3 to 4 months in children taking ARV drugs. Some experts monitor CD4 cell counts and HIV RNA levels less frequently in children and youth who are adherent to therapy and have sustained viral suppression and stable clinical status for more than 2 to 3 years. Table 15 provides one proposed monitoring schedule, which should be adjusted based on the specific therapy a child is receiving. Assessments should include basic hematology, chemistry, CD4 cell 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 urinalysis and serum creatinine may be desirable in children receiving tenofovir, or of serum glucose and lipids in patients receiving protease inhibitors (PIs). Children who develop symptoms of toxicity should have appropriate laboratory evaluations (such as evaluation of serum lactate in a child receiving nucleoside reverse transcriptase inhibitor [NRTI] drugs who develops symptoms suspicious for lactic acidosis) performed more frequently until the toxicity resolves.

For further details of adverse effects associated with a particular ARV, see Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.

Based on accumulated experience with currently available assays, viral suppression is currently defined as an HIV RNA level below the detection limit of the assay used (generally <20–75 copies/mL). This definition of suppression has been much more thoroughly investigated in HIV-infected adults than in HIV-infected children (see *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*).[1] Temporary viral load elevations or "blips" between the level of detection and 1,000 copies/mL often are detected in adults (and children) on ART and should not be considered "virologic failure." For definitions and management of virologic treatment failure, see Management of Treatment-Experienced Infants, Children, and Adolescents.

Table 15. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 1 of 2)

	Entry Into Care	Monitoring Pre-Therapy[1]	ART Initiation[1]	1–2 Weeks on Therapy[2]	4–8 Weeks on Therapy	Every 3–4 Months[3]	Every 6–12 Months	ARV Switch
Clinical History Physical Exam[2]	X	X	X	X	X	X	X	X
CBC w/ Differential	X	X	X		X	X		X
Chemistries[4]	X		X		X[4]	X		X
Electrolytes	X		X			X		X
Glucose	X		X			X		X
AST/ALT	X	X	X	X[5]	X[5]	X		X
Bilirubin	X		X			X		X
BUN/Creatinine	X	X	X			X		X
Albumin/Total Protein	X		X				X	X
Ca/Phosphate	X		X				X	X
CD4 Count/%	X	X	X		X[6]	X		X
HIV RNA	X	X	X	X[2]	X	X		X

Table 15. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 2 of 2)

	Entry Into Care	Monitoring Pre-Therapy[1]	ART Initiation[1]	1–2 Weeks on Therapy[2]	4–8 Weeks on Therapy	Every 3–4 Months[3]	Every 6–12 Months	ARV Switch
Resistance Testing	X							X
Adherence Evaluation			X	X	X	X		X
Lipid Panel	X		X				X	
Urinalysis	X		X				X	

[1] When therapy is started within 30 to 45 days of a Monitoring Pre-Therapy lab result, repeat testing may not be necessary.

[2] Children starting a new ARV 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 that they are adhering to the regimen. Many clinicians will plan additional contacts (in person or by telephone) with children 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 early assessment of response/adherence to therapy.

[3] For children who are in a stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months) many clinicians are considering 6-month intervals between monitoring lab tests. Some clinicians find value in visits every 3 months even when lab testing is not performed (such as to review adherence and update dosing for interim growth).

[4] Some ARV drugs, such as nevirapine and tenofovir, require a specific schedule frequency based on toxicity profile (see specific antiretroviral agents).

[5] In children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.

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

Key to Abbreviations: ARV = antiretroviral, CBC = complete blood count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen

Reference

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. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on August 17, 2012.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents

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

Panel's Recommendations

- Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent **(AIII)**.
- Appropriate dosing of ART for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and pubertal development **(AII)**.
- Effective and appropriate methods should be selected to reduce the likelihood of unintended pregnancy and to prevent secondary transmission of HIV to sexual partners **(AI)**.
- Providers should be aware of potential interactions between ART and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**.
- Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.
- Adolescent girls who require treatment with efavirenz should undergo pregnancy testing before initiation of treatment and receive counseling about potential fetal risk and desirability of avoiding pregnancy while receiving efavirenz-containing regimens **(AIII)**.
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

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 therapy (ART) treatment history.[1] Adolescents with non-perinatally acquired HIV infection generally follow a clinical course similar to that in adults. Because non-perinatally infected adolescents are usually at the initial stages of their HIV disease, they are potential candidates for early intervention and treatment.[2]

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 (PK), 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.[3] Dosages of medications for HIV infection and

opportunistic infections are prescribed according to Tanner staging of puberty[4] rather than strictly on the basis of age.[2] Using the Tanner method, adolescents in early puberty (i.e., Tanner stages I and II) are administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner stage V) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug PK, and dosing of antiretroviral (ARV) drugs during Tanner stages III and IV may be more challenging. Puberty may be delayed in children who were infected with HIV perinatally,[5] adding to discrepancies between Tanner stage-based and age-based dosing, although delayed onset of puberty appears to be uncommon in those in whom potent combination ART was initiated at an early age.[6]

Many ARV drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some protease inhibitors [PIs]) are administered to children at higher weight- or surface area-based doses than would be predicted by direct extrapolation of adult doses. This is based upon reported PK data indicating more rapid 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 ARV drug in adolescents are not available. Appendix A: Pediatric Antiretroviral Drug Information includes a discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

HIV-infected adolescents may be sexually active regardless of how they acquired the virus. Reproductive plans including preconception care, contraception methods, and safer sex techniques for prevention of secondary HIV transmission should be discussed with them regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use).[7] For additional information please 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* (Preconception Care and Reproductive Options for HIV-Concordant and Serodiscordant Couples section).[8]

The possibility of an unplanned pregnancy should also be considered when selecting an ART regimen for an adolescent female. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. In addition, concerns about specific ARV drugs and birth defects should be addressed immediately to preclude misinterpretations or lack of adherence by adolescents with unexpressed plans for pregnancy.[9] For additional information please see 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* (Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants: Teratogenicity section).[8] Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health.

Contraceptive-Antiretroviral Drug Interactions

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter metabolism of 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) (http://www.hiv-druginteractions.org/).[10-12] These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related adverse effects. Some newer agents, such as integrase inhibitors (specifically raltegravir), appear to have no interaction with estrogen-based contraceptives.[13] Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving ART with such interactions.

Whether interactions with ART would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medoxyprogesterone acetate [DMPA]) is unknown 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 in women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional adverse effects, and no clinically significant changes in ARV drug levels.[14, 15] At this time, concerns about loss of bone mineral density (BMD) with long-term use of DMPA with or without ART (specifically tenofovir)[16] should not preclude use of DMPA as an effective contraceptive. However, more active monitoring of BMD in young women on DMPA may need to be considered.[16] Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., the patch and vaginal ring).[17] Intrauterine device (IUD) use while on ART is not restricted by current guidelines; however, IUD users with AIDS should be closely monitored for pelvic infection.[7] Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with ART use during pregnancy (see 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).[8]

HIV-Infected Pregnant Adolescents and Outcomes

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of perinatal transmission and 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 ART 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.[8] Although information is limited about the pregnancies of adolescents who were HIV-infected perinatally, perinatal HIV transmission outcomes in this population appear similar to those in adult cohorts;[18-21] however, there may be differences in pregnancy-related morbidities. Kenny et al[22] reported pregnancy outcomes from the United Kingdom and Ireland in a group of 30 adolescents who were perinatally HIV-infected or who acquired HIV infection at a young age. Few of these pregnancies were planned and in many cases, the partner was unaware of the mother's HIV status. Rates of elective termination, miscarriage, and prematurity were high. The rate of prematurity was twice that in the general adolescent population of Europe. Many of the women had an AIDS diagnosis before pregnancy, but only one infant was HIV-infected. Although the rate of perinatal transmission is reassuring, this study highlights some of the major challenges in caring for pregnant, perinatally HIV-infected youth.

Comparisons of pregnancy incidence and outcomes between perinatally infected and non-perinatally infected youth are few and may offer special insight into the effects of prolonged HIV infection on pregnancy-related sequelae. Agwu et al[23] retrospectively evaluated pregnancies at four clinics. Non-perinatally infected youth were more likely to have one or more pregnancies despite similar age at first pregnancy between groups. They also appeared to have more premature births and spontaneous abortions, but that is tempered by the fact that the perinatally infected youth were more likely to have an elective termination. The perinatal transmission rate for the entire cohort was 1.5%. Similar results were found in several other studies.[24, 25] However, in a single-center review of perinatal versus non-perinatal birth outcomes, infants born to women with perinatal HIV infection were more likely to be small for gestational age, indicating the potential for future adverse health outcomes.[26]

Transition of Adolescents into Adult HIV Care Settings

Facilitating a smooth transition of adolescents with chronic health conditions from their pediatric/adolescent medical home to adult care can be difficult and is especially challenging for HIV-infected adolescents.

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."[27] Care models for children and adolescents with perinatally acquired HIV tend to be family-centered, consisting 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 under the adult HIV care medical model, an adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers with whom he or she often does not have a long-standing relationship. Providing an adolescent and an adult medical care provider with support and guidance regarding expectations for each partner in the patient-provider relationship may be helpful. In this situation, it may also be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time. Providers should also have a candid discussion with a transitioning adolescent to understand what qualities the adolescent considers most important in a provider (such as confidentiality, small clinic size, after-school appointments). Some general guidelines about transitional plans and who might benefit most from them are available.[28-32] Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care.

Outcomes are variable in young adult patients transitioned to adult care. Definitions of "successful transition" have ranged from the ability to maintain a certain level of follow-up in the new clinic, to laboratory measures of stability, to comparisons of younger and older adult patients.[33-35] Factors that should be taken into consideration during transition include social determinants such as developmental status, behavioural/mental health issues, housing, family support, employment, recent discharge from foster care, peer pressure, illicit drug use, and incarceration. Currently there is no definitive model of transition to adult care, but in one study, adherence to medical visits just prior to the transition was predictive of successful transfer.[33] Psychiatric co-morbidities and their effective management also predict adherence to medical care and therapy.[36, 37] With more perinatally infected children surviving into adulthood, transitioning these patients to adult care settings remains challenging.

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again before 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 ART (such as 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*)**.
- To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care **(AII*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Background

Adherence is a determinant of viral suppression and fundamental to successful antiretroviral therapy (ART).[1-4] Prospective adult and pediatric studies have shown a direct correlation between risk of virologic failure and proportion of missed doses of antiretroviral (ARV) drugs.[5] Based on early work in populations of adults primarily being treated with nonboosted protease inhibitor (PI)-based regimens,[2] 95% adherence has been the threshold associated with complete viral suppression. Recent findings from adult populations suggest that the relationship between ARV adherence and viral suppression may vary with individual drug, drug class, and pattern of adherence.[6] Viral suppression can be achieved with lower levels of adherence when using boosted PI and non-nucleoside reverse transcriptase inhibitor regimens.[6, 7] In patients who achieve suppression, the longer the duration of suppression the lower the level of adherence necessary to prevent viral rebound.[8] Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy, depending on the drug combination.[9, 10]

Subtherapeutic ARV drug levels resulting from poor adherence may facilitate development of drug resistance to one or more drugs in a given regimen, and possibly cross-resistance to other drugs in the same class. Multiple factors (including regimen potency, pharmacokinetics, viral fitness, and the genetic barrier to ARV resistance) influence the adherence-resistance relationship.[11] In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens in patients who develop drug-resistant viral strains and in transmission of HIV to sexual partners.

Evidence indicates that adherence problems are common in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics.[3, 4, 12-14] A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial and behavioral characteristics of children and parents, have been associated with adherence; however, no clear predictors of either good or poor adherence in children have been consistently identified.[12, 15-19] Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.[20] 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 and family factors, and characteristics of health care providers.[17] Limited availability of palatable formulations for young children is especially problematic.[5, 21] 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 a 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.[22, 23] Some caregivers may place too much responsibility for managing medications on older children before the children are developmentally able to take on such tasks,[24] whereas others may face health and adherence challenges related to HIV infection or other medical conditions. Many other barriers to adherence exist for HIV-infected children. For example, caregivers' unwillingness to disclose a child's HIV infection status to the child and to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, avoidance of social support, and a tendency for doses to be missed if the parent is unavailable. Furthermore, adherence also may be jeopardized by social issues within a family, such as illicit substance abuse, unstable housing, and involvement with the criminal justice system.

Specific Adherence Issues in Adolescents

HIV-infected adolescents also face specific adherence challenges.[25, 26] Several studies have identified pill burden as well as lifestyle issues (that is, not having medications on hand when away from home, change in schedule) as barriers to complete adherence.[15, 27] Denial and fear of their HIV infection is common in adolescents, especially youth who have been recently diagnosed; this may lead to refusal to initiate or continue ART. Distrust of the medical establishment, misinformation about HIV, and lack of knowledge about the availability and effectiveness of ARV treatments all can be barriers to linking adolescents to care and maintaining successful ART. 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 also has been identified as a barrier to adherence in adolescents.[28] Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness because of lack of familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease all correlate with nonadherence.[25, 29] In a study of 833 HIV-infected Medicaid beneficiaries aged 12 to 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 poorer adherence.[30] In a cross-sectional study of youth perinatally infected with HIV, no significant differences in the frequency of mental health disorders were found between adherent and nonadherent participants.[31] A review of published papers on adherence among HIV-infected youth, however, suggests that

depression and anxiety have been consistently associated with poorer adherence.[29] 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 adolescents who are homeless and have no place to store medicine. When recommending treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ARV regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to ART have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers, cellphones, and alarm devices, are well accepted by some youth. Small, inconspicuous pillboxes may be useful for storing medications in an organized fashion. 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; however, the effect was not sustained at follow-up. Although pager messaging was not associated with reported adherence, improved biologic outcomes were measured.[32] 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 in youth taking ART. However, reduction in viral load was not maintained at 9 months.[33]

Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom ART initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by children and their families and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership with a child and family regarding 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 a patient's explicit agreement with the treatment plan, including strategies to support adherence. Also, it is important to alert patients to minor side effects of ARV drugs, such as nausea, headaches, and abdominal discomfort that may recede over time or respond to change in diet or method and timing of medication administration.

Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations.[14, 34, 35] Both caregivers and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended.[35, 36] 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.[37] Also, targeted questions about stress, pill burden, and daily routine are recommended.[38, 39] Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports.[40] Electronic monitoring devices, such as Medication Event Monitoring System caps, which are equipped with a computer chip that records each opening of a medication bottle, have been shown to be useful tools to measure adherence in some settings.[41-43] Mobile phone technologies, such as interactive voice response and text messaging, are being evaluated to quantify missed doses and provide real-time feedback on adherence to caregivers, but studies in the pediatric population are in the pilot phase.[44] Home visits can play an important role in assessing adherence. In some cases, suspected nonadherence is confirmed only when dramatic clinical responses to

ART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence[45] and drug concentrations in hair are now being studied as an alternative method to measure adherence.[46, 47]

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 children and their 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.[48]

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, as often as weekly during the first month of treatment, 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 (such as 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.[24, 49, 50] Programs designed for administration of 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.[51-53] Modified directly observed therapy (m-DOT), where one dose is administered in a supervised setting and the remaining doses are self-administered, appears to be both feasible and acceptable.[49, 54] However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that it was no more effective than self-administered treatment.[55] In another meta-analysis of DOT studies, DOT was found to have a demonstrated effect on virologic, immunologic, and adherence outcomes, but efficacy of the strategy was not supported when the analysis was restricted to randomized controlled trials.[56] Table 16 summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

Regimen-Related Strategies

ARV regimens often require 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.[57] When nonadherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it can 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. When feasible, once-daily regimens should be prescribed. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV regimens.[58-61] When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can be masked with a small amount of flavoring syrup or food (see Appendix A: Pediatric Antiretroviral Drug Information) or a child can be taught to swallow pills in order to overcome medication aversion.[62]

Child/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV 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 a child's medication adherence. Caregivers should understand that the first ARV 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 an 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.[63, 64] Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children aged 4 to 21 years.[65] Availability of mental health services and treatment of mental health disorders also may facilitate adherence to complex ARV regimens. A gastrostomy tube can be considered for nonadherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications.[66] If adequate resources are available, home nursing interventions also may be beneficial.[67] Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children, 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 patients' cell phone alarms to go off at medication times; providing pill boxes and other adherence support tools; weekly filling of pill boxes by nursing or pharmacy staff, particularly for patients with complex regimens; and home delivery of medications. Two recent studies conducted in adults in Kenya found that individuals who received cell phone text messages had significantly improved ART adherence. In one study, ART-naive adults initiating treatment received weekly short message service (SMS) from a clinic nurse and were required to respond.[68] Self-reported adherence and rates of HIV-1 viral suppression at 12 months were significantly greater in individuals randomized to SMS compared with standard-of-care adherence support. Similarly, in second study, adult participants who received weekly SMS reminders were more likely to achieve high levels of adherence and less likely to experience treatment interruptions.[69]

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with families. This process begins early in a provider's relationship with a 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.[70, 71] 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 also has been shown to improve treatment outcomes.[72]

Table 16. Strategies to Improve Adherence to 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, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat mental health issues before starting antiretroviral (ARV) drugs, if possible.
• Identify family, friends, health team members, or others who can support adherence.
• 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 ARV drug (that is, 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 associated with demands to attain 95% adherence with medication doses.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, alarms, pagers, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages 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, such as medication education and counseling, refill reminders, and home delivery of medications.
• Consider gastrostomy tube use in selected circumstances.
• Consider directly observed therapy (DOT) at home, in the clinic, or during a brief inpatient hospitalization.

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Management of Medication Toxicity or Intolerance (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- In children who have severe or life-threatening toxicity, all components of their drug regimen should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, antiretroviral therapy (ART) should be resumed with substitution of a different antiretroviral (ARV) drug or drugs for the offending agent(s) **(AII*)**.
- When modifying therapy because of toxicity or intolerance to a specific drug in children in whom virus has been suppressed, changing one drug in a multidrug 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 ARV toxicity, except when therapeutic drug monitoring (TDM) indicates a drug concentration above the normal therapeutic range **(AII*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Overview

Side effects from or intolerance to antiretroviral (ARV) agents are common in children and should prompt a re-evaluation of the ARV regimen. Drug-related toxicity can be acute, occurring soon after a drug has been administered; subacute, occurring within 1 to 2 days of administration; or late, occurring after prolonged drug administration. For some ARV medications, pharmacogenetic markers associated with risk of early treatment discontinuation because of toxicity have been identified, but the only such screen in clinical use is HLA B*5701 as a marker for abacavir hypersensitivity.[1] The differential diagnosis of drug toxicity includes toxicity due to HIV infection or other infections or conditions, bone marrow suppression with disseminated *Mycobacterium avium* complex (MAC) infection, and anemia due to blood loss from cytomegalovirus colitis. ARV drug-related adverse events can vary in severity from mild to severe and life threatening (see Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations).

Identification of the responsible agent may allow for substitution of a similar agent that recent HIV drug-resistance testing predicts will be active against a patient's virus. Knowledge of a patient's ARV history and viral resistance profile before the current course of antiretroviral therapy (ART) is essential. Any new agent used should be assessed for likely effectiveness against a patient's virus and for possible interactions with other medications the patient will take.

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

Physicians, patients, and caregivers should discuss the response to medication-related toxicity, taking into

account its severity, the relative need for viral suppression, and the available ARV options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution. However, even mild adverse effects may have a negative impact on medication adherence and should be discussed before therapy is initiated, at regular provider visits, and at onset of any adverse effects. Common, self-limited adverse effects should be anticipated. For example, when initiating therapy with boosted protease inhibitors (PIs) many patients experience gastrointestinal (GI) adverse effects such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these side effects. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system (CNS) adverse effects are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime to help minimize these adverse effects and be advised that these side effects should diminish or disappear within 2 to 4 weeks of initiating therapy. In addition, mild rash can be treated with drugs such as antihistamines. For some moderate toxicities, using a drug in the same class as the one causing toxicity 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 ARV drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity). Once the patient is stable and toxicity has resolved, another drug can be substituted for the drug associated with the toxicity.

In patients who experience an unacceptable adverse effect from ART, every attempt should be made to identify the offending agent and replace the drug with another effective agent as soon as possible.[2, 3] For example, if therapy needs to be stopped because of a severe or life-threatening side effect, all ARV drugs should be stopped at the same time. Once the offending drug or alternative cause for the adverse event has been determined, planning can begin for resumption of therapy with a new ARV 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 ARV regimen should then be started simultaneously, rather than one at a time with observation for adverse effects. Many experts recommend stopping efavirenz, etravirine, or nevirapine before stopping other drugs, if possible, because these drugs have significantly longer half-lives than nucleoside reverse transcriptase inhibitors (see Discontinuation or Interruption of Therapy section). However, in patients who have 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.[4-8] 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 multidrug regimen is a permissible for patients whose viral loads are undetectable. However, substitution of a single active agent for a single drug in a failing multidrug regimen is generally not recommended because of 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 it is useful are unclear, especially in children. One such setting, however, may be in the context of the child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In this situation, it is reasonable for a clinician to use TDM (if available) to determine if the toxicity is result of a drug concentration exceeding the normal therapeutic range.[9, 10] 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.

To summarize, 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 a patient's virus is sensitive (such as

changing to abacavir for zidovudine-related anemia or to nevirapine for efavirenz-related CNS symptoms).

- Change drug class, if necessary (such as from a PI to a non-nucleoside reverse transcriptase inhibitor or vice versa) and if a patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations describe specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, renal toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, GI adverse effects, CNS adverse effects, peripheral neuropathy, 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.

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Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Global CNS depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	Onset: 1–6 days after starting LPV/r Presentation: Neonates/preterm infants: global CNS depression, cardiac toxicity, respiratory complications	Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period.
Neuropsychiatric symptoms and other CNS manifestations	EFV	Onset: 1–2 days after initiating treatment Most symptoms subside or diminish by 2–4 weeks (but may persist in a minority of patients) Presentation: May include one or more of the following: dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, suicidal ideation, seizures (including absence seizures) CNS side effects may be more difficult to detect in children because neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders may be difficult to assess.	Variable, depending on age, symptom, assessment method Children: 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation Adults: >50% for any CNS manifestations of any severity 2% for EFV-related severe CNS manifestations	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level >4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug discontinuation.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
	RAL	Presentation: Increased psychomotor activity, headaches, insomnia, depression	Children: Psychomotor activity reported in one child Adults: Headache, insomnia (<5% in adult trials)	Elevated RAL concentrations Prior history of insomnia or depression	Use with caution in the presence of drugs that increase RAL concentration	Consider drug discontinuation in case of severe insomnia.
Intracranial hemorrage	TPV	Onset: 7–513 days after starting TPV	Children: No cases of ICH reported in children Adults: In premarket approval data in adults, 0.23/100 patient-years or 0.04–0.22/100 patient-years in a retrospective review of 2 large patient databases	Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.
Cerebellar ataxia	RAL	Onset: As early as 3 days after starting RAL Presentation: Tremor, dysmetria, ataxia	Two cases reported in adults during post marketing period	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (such as drug-drug interaction) identified and removed.

Key to Acronyms: ARV = antiretroviral, CNS = central nervous system, CYP = cytochrome P, EFV = efavirenz, ICH = intracranial hemorrhage, LPV/r = lopinavir/ritonavir, RAL = raltegravir, TDM = therapeutic drug monitoring, UGT = uridine diphosphate-glucurononyl transferase, TPV = tipranavir, ATV = atazanavir

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Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (page 1 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Dyslipidemia	PIs: All PIs; lower incidence with ATV and DRV NRTIs: Especially d4T NNRTIs: RPV < EFV	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 ART will have lipoprotein abnormalities.	HIV infection High-fat, high-cholesterol 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, non-HDL-C, LDL-C, and TG before initiating or changing ART, then every 6 months, and thereafter, every 6–12 months. *Children (aged ≥2 years) without lipid abnormalities or additional risk factors:* Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. 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, and LDL-C before initiating or changing therapy and every 6 months thereafter (or more often if indicated). *Children receiving lipid-lowering therapy with statins or fibrates:* Obtain fasting (12-hour) lipid profiles, LFTs, and CK before initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal alterations in AST, ALT, and CK, repeat tests every 3 months. Also repeat tests 4 weeks after increasing doses of antihyperlipidemic agents.	Counsel lifestyle modification (low-fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). Switch to a new ART regimen less likely to cause lipid abnormalities.[a] Pharmacologic Management: Initiate drug therapy promptly in patients with TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.[b] Ezetimibe may be considered in addition to statins.[c] Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children. No consensus as to what LDL-C should prompt treatment in children receiving ARVs.[d] HIV-infected patients are considered to be at moderate risk of CVD. Assessment of additional risk factors should be done in all patients.[e] *High-risk patients:* Goal LDL-C ≤100 mg/dL. *Moderate-risk patients:* Goal LDL-C ≤130 mg/dL. *At-risk patients:* Goal LDL-C ≤160 mg/dL.

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

[a] 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.

[b] Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins is limited to children >6 years of age.

[c] In general, recommend using in boys aged ≥10 years and in girls preferably after onset of menses. Treatment with statins in children ≤10 years of age is limited to those with severe primary hyperlipidemia, a high-risk condition, or evident CVD, all under the care of a lipid specialist. Multiple drug interactions exist between ARVs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin (Pravachol®), atorvastatin (Lipitor®), rosuvastatin (Crestor®), fluvastatin (Lescol®), and ezetimide (Zetia®) are approved for use in children ≥10 years of age.

[d] The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children is likely to lead to premature CVD.

[e] Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

Key to Acronyms: ALT = alanine transaminase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, ART = antiretroviral therapy, CK = creatine kinase, CVD = cardiovascular disease, d4T = stavudine, EFV = efavirenz, HDL-C = high-density lipoprotein cholesterol, non-HDL-C= non-high-density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, LFT = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PUFA = polyunsaturated fatty acid, RPV = rilpivirine, TC = total cholesterol, TG = triglycerides

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Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs	Onset: Early Presentation: Nausea, emesis—may be associated with anorexia and/or abdominal pain	Varies with ARV agent. 10%–30% in some series.	Unknown	Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/ caretaker that nausea and vomiting will likely decrease over time. Provide supportive care including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (NFV, LPV/r, FPV/r), buffered ddI	Onset: Early Presentation: Generally soft, more frequent stools	Varies with ARV agent. 10%–30% in some series.	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment for ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate, bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful.
Pancreatitis	ddI (especially with concurrent d4T or TDF); reported, albeit rarely, with most ARVs	Onset: Any time, usually after months on therapy Presentation: Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<1%–2% in recent series. Frequency was higher in the past with higher dosing of ddI.	Concomitant treatment with other medications associated with pancreatitis (such as TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia	Avoid use of ddI in patients with history of pancreatitis.	Discontinue offending agent. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddI = didanosine, FPV/r = fosamprenavir/ritonavir, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, TDF = tenofovir disoproxil fumarate, TG = triglyceride, TMP-SMX = trimethoprim sulfamethoxazole, ZDV = zidovudine

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Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Anemia[a]	Principally ZDV	Onset: Variable, weeks to months Presentation: Most commonly asymptomatic or mild fatigue, pallor, tachypnea; rarely, congestive heart failure	HIV-exposed newborns: Severe anemia uncommon, but may be seen coincident with physiologic Hgb nadir HIV-infected children on ARVs: 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV	HIV-exposed newborns: Premature birth *In utero* exposure to ARVs Advanced maternal HIV Neonatal blood loss Concurrent ZDV + 3TC neonatal prophylaxis HIV-infected children on ARVs: Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) Iron deficiency Advanced or poorly controlled HIV disease	HIV-exposed newborns: Monitor CBC at birth. Consider repeat CBC at 4 weeks for neonates who are at higher risk (such as those born prematurely or known to have low birth Hgb). HIV-infected children on ARVs: Avoid ZDV in children with moderate to severe 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 g/dL or anemia is associated with symptoms. Consider discontinuing ZDV if 4 weeks or more of 6-week ZDV prophylaxis regimen are already completed (see Perinatal Guidelines[b]). HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs, if feasible. Treat coexisting iron deficiency, OIs, malignancies. For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin.

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Neutropenia[a]	Principally ZDV	Onset: Variable Presentation: Most commonly asymptomatic	HIV-exposed newborns: Rare HIV-infected children on ARVs: 9.9%–26.8% of children on ARVs, depending upon the ARV regimen Highest rates with ZDV-containing regimens	HIV-exposed newborns: *In utero* exposure to ARVs Concurrent ZDV + 3TC neonatal prophylaxis HIV-infected children on ARVs: Advanced or poorly controlled HIV infection Myelosuppressive drugs (such as TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-infected children on ARVs: Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/μL, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see Perinatal Guidelines[b]). HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs if feasible. Treat coexisting OIs, malignancies. For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF.

[a] HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

[b] *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 Acronyms: 3TC = lamivudine, ANC = absolute neutrophil count, ARV = antiretroviral, CBC = complete blood count, G6PD = glucose-6-phosphate dehydrogenase, G-CSF = granulocyte colony-stimulating factor, Hgb = hemoglobin, NRTI = nucleoside reverse transcriptase inhibitor, OIs = opportunistic infections, TMP-SMX = trimethoprim-sulfamethoxazole, ZDV = zidovudine

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Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Hepatic toxicity (elevated AST, ALT, clinical hepatitis)	All ARVs (NVP, TPV of particular concern)	Onset: *NNRTI and PI therapy:* Within 12 weeks of initiation. *NRTI therapy:* Within months to years of initiation. *Any ARV combination regimen:* Early due to IRIS. Presentation: Asymptomatic elevation of AST, ALT. May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. AST, ALT elevations while on NVP, ABC, or RAL may be associated with skin rash or a hypersensitivity reaction. HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, and TDF. NRTIs, especially ZDV, ddI, and d4T, may be associated with lactic acidosis and hepatic steatosis.	Uncommon in children. Frequency varies with different agents and drug combinations.	HIV infection HBV or HCV coinfection Elevated baseline ALT, AST Other hepatotoxic medications Alcohol use Underlying liver disease Pregnancy For NVP-associated hepatic events in adults: Female with pre-NVP CD4 count >250 cells/mm^3 Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV	Prevention: Avoid concomitant use of hepatotoxic medications. If hepatic enzymes are elevated >5–10 times ULN, most clinicians would avoid NVP. Monitoring: *For ARVs other than NVP:* Obtain AST, ALT at baseline and thereafter at least every 3–4 months or more frequently in at-risk patients (such as HBV- or HCV-coinfected or elevated baseline AST, ALT). *For NVP:* Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.	If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP hypersensitivity). In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy and monitor patient closely. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent. When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, and ZDV, d4T, and ddI in particular (see also lactic acidosis). Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Indirect hyperbilirubinemia	IDV, ATV	Onset: Early in therapy Presentation: Jaundice; Asymptomatic elevation of indirect bilirubin levels with normal direct bilirubin, AST, and ALT.	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: No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).
Non-cirrhotic portal hypertension	ARVs, especially ddI, d4T and combination of ddI and d4T	Onset: Late in therapy Presentation: GI bleeding, esophageal varices, hypersplenism. Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism). Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis	Rare: Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: No specific monitoring.	Manage complications of GI bleeding and esophageal varices.

[a] HLA-DRB1*0101 in Caucasians, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and Caucasians

Key to Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine transaminase, ALP = alkaline phosphatase, ARV = antiretroviral, 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, IRIS = immune reconstitution inflammatory syndrome, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, TPV = tipranavir, ULN = upper limit of normal, ZDV = zidovudine

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Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, DM[a]	Thymidine analogue NRTIs (d4T, ddI, ZDV) Some PIs (IDV, LPV/r; perhaps less often ATV, ATV/r, DRV/r, TPV/r)	Onset: Weeks to months after beginning therapy; median of 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:* 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) *ARV-treated children:* Very rare in HIV-infected children	Risk factors for Type 2 DM: Lipodystrophy Metabolic syndrome Family history of DM High BMI Obesity	Prevention: Lifestyle modification (see Management). Although uncertain, avoiding use of d4T, IDV may reduce risk. Monitoring: Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans. *Obtain RPG levels at*: Initiation of ARV therapy; 3–6 months after therapy initiation; and once a year thereafter. For RPG ≥140 mg/dL, obtain FPG performed after 8-hour fast and consider referral to endocrinologist.	Counsel on 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:* Patient meets diagnostic criteria for DM; consult endocrinologist. *FPG 100–125 mg/dL:* Impaired FPG is suggestive of insulin resistance; consult endocrinologist. *FPG <100 mg/dL:* Normal FPG but does not exclude insulin resistance; recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a standard OGTT; and *diabetes mellitus* as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an 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, HgbA1C, 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 Acronyms: ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, d4T = stavudine, ddI = didanosine, DM = diabetes mellitus, DRV/r = darunavir/ritonavir, FPG = fasting plasma glucose, IDV = indinavir, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, OGTT = oral glucose tolerance test, PG = plasma glucose, PI = protease inhibitor, RPG = random plasma glucose, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (alone and in combination)	Onset: 1–20 months after starting therapy (median onset 4 months in 1 case series). Presentation: Usually insidious onset of a combination of signs and symptoms: generalized fatigue, weakness, and myalgias; vague abdominal pain, weight loss, unexplained nausea or vomiting; dyspnea; peripheral neuropathy. Patients may present with acute multi-organ failure (such as fulminant hepatic, pancreatic, and respiratory failure).	Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L): *Adults:* 15%–35% of adults receiving NRTI therapy for longer than 6 months *Children:* 29%–32% Symptomatic severe hyperlactatemia (>5.0 mmol/L): *Adults:* 0.2%–5.7% Symptomatic lactic acidosis/hepatic steatosis: Rare in all age groups (*1.3–11 episodes per 1,000* person-years), but associated with a high fatality rate (33%–58%)	Adults: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (such as d4T, TDF, RBV, or tetracycline) • Coadminstration of TDF with metformin • Overdose of propylene glycol • CD4 T lymphocyte count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly, pregnancy Pre-term infants: • Use of propylene glycol (e.g., as an diluent for LPV/r)	Prevention: Avoid d4T and ddI in combination. Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring: *Asymptomatic:* Measurement of serum lactate is not recommended. *Clinical signs or symptoms consistent with lactic acidosis:* Obtain blood lactate level;[a] 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 workup. Lactate >5.0 mmol/L (confirmed with second test)[b] 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, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C). Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and monthly monitoring of lactate for at least 3 months.

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

[b] Management can 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, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, RBV = ribavirin, TDF = tenofovir disoproxil fumarate, THAM = tris–hydroxymethyl-aminomethane

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Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lipodystrophy (fat redistribution)—general information	See below for specific associations.	Onset: Trunk and limb fat initially increases within a few months of start of ART; peripheral fat wasting may not begin to appear for 12 to 24 months.	Adults: 2%–84% Children: 1%–33%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART	See below	See below
Central lipohypertrophy	Can occur in the absence of ART, but most associated with PIs and EFV; EFV also associated with gynecomastia and breast hypertrophy	Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Up to 25%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: Calorically appropriate, low-fat diet and exercise. Monitoring: Measure BMI.	Calorically appropriate, low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: recombinant human growth hormone, growth hormone-releasing hormone, metformin, thiazolidinediones, anabolic steroids, or liposuction.
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 (up to 15%) in patients not treated with d4T or ZDV	d4T and ZDV Obesity before 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. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: injections of poly-L-lactic acid, recombinant human leptin, autologous fat transplantation, or thiazolidinediones.

Key to Acronyms: ARV = antiretroviral, BMI = body mass index, ART = antiretroviral therapy. CVD = cardiovascular disease, d4T = stavudine, DXA = dual energy x-ray absorptiometry, EFV = efavirenz, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ZDV = zidovudine

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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.

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Table 17i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Urolithiasis/ nephrolithiasis	IDV, ATV	Onset: Weeks to months after starting therapy Clinical findings: Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%). ATV nephrolithiasis rare	In adults, high serum IDV concentrations and elevated urine pH (>5.7) associated with persistent pyuria. Unknown in children.	Prevention: Maintain adequate hydration. Monitoring: Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV agent.
Renal dysfunction	TDF	Onset: Variable; in adults, weeks to months after initiation of therapy. Hypophosphatemia appears at a median of 18 months. Presentation: Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria	Adults: ~2% with increased serum creatinine; ~0.5% with severe renal complications Children: ~4% with hypophosphatemia or proximal tubulopathy; 25% to 78% with severe proteinuria (may be confounded by advanced HIV infection in children studied, and concomitant use of ddI)	Risk may be increased in children aged >6 years, black race, Hispanic/Latino ethnicity, and by advanced HIV infection, concurrent use of ddI or PIs (especially LPV/r), and pre-existing renal dysfunction).	Urinalysis, measurement of serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months.	If TDF is the likely cause, consider using alternative medication.
	IDV	Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If IDV is likely cause, consider using alternative medication.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, ddI = didanosine, IDV = indinavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate

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Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia, Osteoporosis, Osteonecrosis (page 1 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Osteopenia and osteoporosis	cART, especially following initiation of cART, regardless of regimen. Specific agents of possible concern: TDF, d4T, and PIs	Onset: Any age; greatest risk in months after initiation of associated ARV. Presentation: Most commonly asymptomatic; fracture (rare). Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.	Low BMD: 20% of children treated with cART had BMD *z* score < -1.5.	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Corticosteroid use Medroxyprogesterone use	Prevention: Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Minimize modifiable risk factors (smoking, low BMI, steroid use). Monitoring: Assess nutritional intake (calcium, vitamin D, and total calories). Obtain serum 25-OH-vitamin D.[a] Obtain DXA.[b]	Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Reduce modifiable risk factors (smoking, low BMI, use of 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: Obtain plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high. Treatment: *Early stages:* Decrease weight bearing on affected joint and use analgesic. Limited evidence for use of bisphosphonates. *Later stages:* Consider surgical intervention.

Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia, Osteoporosis, Osteonecrosis (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

[a] Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth because, in this population, the prevalence of vitamin D insufficiency is high.

[b] 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 prepubertal children and children in early puberty who are initiating treatment with tenofovir. DXA should also be obtained in children with indications not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ARVs = antiretrovirals, BMD = bone mineral density, BMI = body mass index, cART = combination antiretroviral therapy, CT = computed tomography, d4T = stavudine, DXA = dual energy x-ray absorptiometry, MRI = magnetic resonance imaging, PIs = protease inhibitors, TDF = tenofovir disoproxil fumarate

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Osteopenia and Osteoporosis

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Table 17k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency [a]	Risk Factors	Prevention/Monitoring	Management
ARV toxic neuropathy[b]	d4T, ddI	Onset: Variable, weeks to months following NRTI initiation Presentation: Decreased sensation Aching, burning, painful numbness Hyperalgesia (lowered pain threshold) Allodynia (non-noxious stimuli cause pain) Decreased or absent ankle reflexes Distribution: bilateral soles of feet, ascending to legs and fingertips	HIV-infected children: 1.13% prevalence (baseline 2001); 0.23 per 100 person-years (2001–2006) 0.07%–0.26% incidence in two large African cohorts (aged 1 month–18 years, median follow-up 1.8–3.2 years) HIV-infected adults: 17%–57% taking d4T	HIV-infected adults: Pre-existing neuropathy (diabetes, alcohol abuse, vitamin B_{12} deficiency) Elevated triglyceride levels Older age Poor nutrition More advanced HIV disease Mitochondrial DNA haplogroup	Limit use of d4T and ddI, if possible. As part of routine care, monitor for symptoms and signs of peripheral neuropathy.	Discontinue offending agent. Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: tricyclic antidepressants, gabapentin, pregabalin, mexilitine, or lamotrigine.

[a] Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

[b] HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddI = didanosine, NRTI = nucleoside reverse transcriptase inhibitor

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Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 1 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash.	Onset: 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 HSR).	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, RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, TPV). • Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP.	• When starting NVP or restarting after interruptions >14 days: Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] Avoid use of corticosteroids during NVP dose escalation. • Assess patient for concomitant medications and illnesses that cause rash, rash severity, mucosal involvement, and presence of systemic signs and symptoms (see also HSR).	*Mild-to-moderate maculopapular rash without systemic or mucosal involvement:* Prescribe antihistamine as needed; ARV medication can be continued.[a] *Severe rash (accompanied by blisters, fever, involvement of the 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. If rash develops with NVP treatment, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).
	ENF	Onset: 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 and children: >90%	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. • Rotate injection sites.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 2 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
SJS/EM major/TEN	Many ARVs, especially NNRTIs (see frequency column)	Onset: First few days to weeks after initiating therapy Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bulla formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case reports: FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ethnicity (black, Asian, Hispanic)	• *When starting NVP or restarting after interruptions >14 days:* Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic HSR (with or without skin involvement and excluding SJS)	ABC	Onset: *With first use:* within first 6 weeks *With reintroduction:* within hours 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. With rechallenge, symptoms can mimic anaphylaxis.	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 medical record should clearly indicate that the patient is ABC allergic. • Counsel patients and 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 within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 3 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	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 without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome has also been described.	4% (2.5%–11%)	Adults: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female gender (Risk is 3-fold higher in females compared with males.) Children: NVP hepatoxicitiy and hypersensitivity are less common in prepubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%.	• 2-week lead-in period for start or restart for interruptions >14 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.[a] • 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, before dose escalation, 2 weeks post dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in postexposure prophylaxis.	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor patient closely. • Do not reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 4 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	ENF, ETR	Onset: Any time during therapy. Presentation: Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARVs. Rechallenge is not recommended.
	RAL	DRESS syndrome	Case report	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARVs. Rechallenge with RAL is not recommended.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.	Discontinue all ARVs. Rechallenge with MVC is not recommended.

[a] The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of 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. NVP should be stopped if the rash is severe or is worsening or progressing.

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

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Management of Treatment-Experienced Infants, Children, and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

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 quantification 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 prevent development of additional drug resistance that could further limit 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 require evaluation for treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

Overview

Although many children remain on stable antiretroviral therapy (ART) for several years,[1-4] reassessment of a therapeutic regimen will often become necessary over time.[5]

Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria. A careful assessment is required to evaluate the etiology of treatment failure and determine the appropriate management strategy. Not all instances of treatment failure require an immediate change in ART; in many cases, treatment efficacy can be restored by improving adherence or addressing other comorbidities. The approach to treatment failure in children and adolescents who have received more than one ARV regimen is often more complex than the approach in those receiving their first regimen. However, with the availability of an increasing number of antiretroviral (ARV) agents, including those directed at new viral targets, the goals of treatment for all patients—whether on initial, second, or subsequent regimens—remain the same: complete virologic suppression, combined with recovery or maintenance of immunologic function, and attainment or preservation of optimal clinical status, while preventing emergence of new viral drug-resistance mutations (see Assessment of Patients with Antiretroviral Treatment Failure and Management of Medication Toxicity or Intolerance). Decisions regarding changing ART should be individualized and should take into consideration a child's treatment history, including any ARV-associated toxicities; current virologic, immunologic, and clinical status; and ability to adhere to a new regimen as well as prior and current detection of drug-resistant virus and available treatment options. Given these complexities, all children being evaluated

for treatment failure should be managed in collaboration with a pediatric HIV specialist.

Developmental and behavioral characteristics distinguish adolescents from adults and affect decisions concerning management of treatment failure (see Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents). Drug metabolism may vary during puberty,[6] 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 (such as atazanavir; see Appendix A: Pediatric Antiretroviral Drug Information). In addition, dosing recommendations for adolescents have not been established for a number of new ARV medications now used in adults. Dosing guidance for children and adolescents for all ARV agents can be found in Appendix A: 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 ARV treatment failure in adolescents.

Definitions of Treatment Failure (see Table 18. Definitions of Treatment Failure in Human Immunodeficiency Virus (HIV)-Infected Children)

Treatment failure can be categorized as virologic failure, immunologic failure, or clinical failure (or some combination of the three). Laboratory results must be confirmed with repeat testing before a final assessment of virologic or immunologic treatment failure is made.

Virologic Failure: Virologic failure occurs as an incomplete initial response to therapy or as a viral rebound after virologic suppression is achieved. Virologic suppression is defined as having plasma HIV RNA below the level of quantification using the most sensitive assay (<20–75 copies/mL). Older assays with lower limits of 200 or 400 copies/mL are acceptable if they are the only option; levels reported as detectable but below the level of quantification should not be considered evidence of virologic failure.

- **Incomplete virologic 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 to 12 weeks of therapy, plasma HIV RNA >200 copies/mL after 6 months of therapy, or repeated plasma HIV RNA greater than the level of quantification using the most sensitive assay after 12 months of therapy. Occasionally, infants with high plasma HIV RNA levels at initiation of therapy have HIV RNA levels that are declining but remain >200 copies/mL after 6 months of therapy. Among many of those receiving lopinavir/ritonavir, suppression can be achieved without regimen change if efforts are made to improve adherence.[7] However, ongoing non-suppression—especially with non-nucleoside reverse transcriptor inhibitor-based regimens—increases risk of drug resistance.[8] HIV-infected adults with detectable HIV RNA and a quantified result <200 copies/mL after 6 months of combination ART (cART) often ultimately achieve virologic suppression without regimen change.[9]
- **Viral rebound:** For children whose plasma HIV RNA level was previously virologically suppressed in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA above the level of quantification. "Blips," defined as isolated episodes of plasma HIV RNA <1,000 copies/mL followed by return to viral suppression, are common and not generally reflective of virologic failure.[10, 11] Repeated or persistent plasma HIV RNA detection above the level of quantification (especially if >1,000 copies/mL) more likely represents viral rebound.[12, 13]

Immunologic Failure: Immunologic failure is defined as an incomplete immunologic response to therapy or an immunologic decline while on therapy. Evaluation of immune response in children is complicated by the normal age-related changes in CD4 T lymphocyte (CD4 cell) count discussed previously (see Immunologic Monitoring in Children). Thus, the normal decline in CD4 values with age needs to be considered when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age. At about age 5 years, absolute CD4 count values in children approach those of adults; consequently, changes in absolute count can be used in children aged ≥5 years.

- **Incomplete immunologic response to therapy:** Incomplete immunologic response to therapy is defined as the failure of CD4 percentage to increase by ≥5 percentage points in a child aged <5 years with severe immune suppression (CD4 percentage <15%) or as the failure of absolute CD4 cell count to increase by ≥50 cells/mm^3 above baseline within the first year of therapy in a child ≥5 years of age with severe immune suppression (CD4 <200 cells/mm^3).
- **Immunologic decline:** Immunologic decline is defined as a sustained decline to 5 CD4 percentage points below the pre-therapy baseline at any age or a decline in absolute CD4 cell count to below pre-therapy baseline in children aged ≥5 years. 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 cell count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in children already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 cell count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Clinical Failure: Clinical failure is defined as the occurrence of new opportunistic infections (OIs) and/or other clinical evidence of HIV disease progression during therapy. Clinical failure 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. Clinical events occurring in the first several months after cART initiation often do not represent cART failure. For example, the development or worsening of an OI in a patient who recently initiated cART may reflect a degree of persistent immune dysfunction in the context of early recovery, or, conversely be a result of immune reconstitution inflammatory syndrome (IRIS). However, the occurrence of significant clinical disease progression, such as noted below, should prompt 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 (e.g., lack of expected increase in head circumference in infants and young children), decline in 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, cART that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of HIV-related illnesses. The converse is also generally true: ineffective cART that fails to suppress viremia is commonly accompanied by immunologic and clinical failure.[14] However, patients may also present with failure in one domain (e.g., immunologic failure) but with a good response in the other domains (e.g., virologic and clinical response). In fact, the discordance in responses to cART can 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 ART failure has truly occurred.

Incomplete Virologic Response Despite Adequate Clinical and Immunologic Responses: Some patients who are maintained on cART may sustain immunologic and clinical benefit for up to 3 years despite

persistent viremia.[15-24] This observation is the rationale for continuing non-suppressive ART for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practical. The risks, benefits, and 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 maintenance of a lower viral load or selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation for this discordance 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 non-progressors" 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 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (such as 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.

In addition, it is common for patients with baseline severe immunosuppression 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 before initiating combination therapy are at higher risk of an impaired CD4 lymphocyte response to cART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.[25-29]

Certain ARV agents or combinations may be associated with a blunted CD4 response. For example, treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced[30] and this combination is not recommended as part of initial therapy. Dosing of didanosine should be adjusted when co-administered with tenofovir. In adults, ARV regimens containing zidovudine may also impair rise in CD4 cell count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine.[31] Fortunately, this ARV drug-related suboptimal CD4 cell count response to therapy does not seem to confer an increased risk of clinical events. It is not clear whether this scenario warrants substitution of zidovudine with another drug.

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis) are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in HIV-uninfected adults.[32]

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression:

Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response

- Lab error (in CD4 lymphocyte or viral load result)
- Normal age-related CD4 lymphocyte decline (i.e., immunologic response not actually poor)
- Low pretreatment CD4 cell count or percentage
- Adverse effects of use of zidovudine or the combination of tenofovir and didanosine
- Use of systemic corticosteroids or chemotherapeutic agents

- Conditions that can cause low CD4 values, such as hepatitis C coinfection, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis

Poor Immunologic and Clinical Responses Despite Virologic Suppression

- Lab error, including HIV strain/type not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
- Persistent immunodeficiency soon after initiation of ART but before ART-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 cART. Not all cases represent ART 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 cART is IRIS, which does not represent cART failure and does not generally require discontinuation of cART.[33, 34] 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 the damaged organs because the immunologic improvement may not reverse damage to the organs.[35] Such cases do not represent cART failure and, in these instances, children would not benefit from a change in ARV regimen. Before reaching a definitive conclusion of cART failure, a child should also be evaluated to rule out (and if indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (such as *Pneumocystis jirovecii* pneumonia 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. Although such cases are rare, they may represent cART failure and suggest that improvement in CD4 values may not necessarily represent the 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)
- New clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Table 18. Definitions of Treatment Failure in HIV-Infected Children

Virologic Failure[a]	• **Incomplete virologic response to therapy:** Incomplete virologic response to therapy is defined as:
	  • <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, or
	  • HIV RNA >200 copies/mL after 6 months of therapy, or
	  • repeated HIV RNA above the level of quantification using the most sensitive assay after 12 months of therapy.[a]
	• **Viral rebound:** Viral rebound is defined as repeated detection of plasma HIV RNA above the level of quantification after a child had achieved virologic suppression in response to therapy. Isolated episodes of plasma HIV RNA detection above the level of quantification but <1,000 copies/mL are common. They generally do not indicate virologic failure and may be transient blips, but should be followed up to confirm spontaneous resolution.

Immunologic Failure[b]	• **Incomplete immunologic response to therapy:** Failure in a child aged <5 years with severe immune suppression (CD4 percentage <15%) of CD4 percentage to increase by ≥5 percentage points or failure in a child aged ≥5 years with severe immune suppression (CD4 < 200 cells/mm^3) of absolute CD4 cell counts to increase 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 pre-therapy baseline at any age or decline to below pre-therapy baseline in absolute CD4 cell count in children aged ≥5 years.[c]
Clinical Failure	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline in cognitive function documented by psychometric testing, and 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.

[a] Children with higher plasma HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.[7] HIV-infected adults with HIV RNA detectable above the level of quantification but <200 copies/mL after 6 months of cART often ultimately achieve virologic suppression without regimen change.[9]

[b] At least 2 measurements (taken at least 1 week apart) should be performed to confirm initial laboratory results.

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

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Assessment of Patients with Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Assess adherence to therapy; address barriers and develop interventions to improve adherence **(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 (ARV) drug exposure that can result in combination antiretroviral therapy failure **(AII)**. • Perform ARV drug-resistance testing when virologic failure occurs, while a patient is still taking the failing regimen and before changing to a new regimen **(AI*)**. • Perform assessment in collaboration with a pediatric HIV specialist **(AI*)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion* *† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents*

Each patient with an incomplete virologic 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. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics (PK) that could result in low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance. The main barrier to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the antiretroviral (ARV) regimen.

Table 19 outlines a comprehensive approach to evaluating causes of virologic 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 in the hospital because history alone may not fully identify the barriers to complete adherence.[1, 2]

Adherence Problems (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—particularly in the presence of susceptible virus—are commonly an indication of poor adherence. Depending on the specific drug regimen, even small lapses in adherence can lead to cART failure.[3-8] Although adherence should be addressed at each medical visit for all children receiving cART, suspicion of treatment failure warrants increased scrutiny of adherence. Patterns of adherence can change over time and may be influenced by a large number of factors inherent to the drugs as well as social and psychological issues of children and their families.

It is important to evaluate whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects in order to determine changes best suited to the individual requirements of a child and his or her family. Family education concerning adherence should be intensive and include training in the administration of prescribed medications with emphasis on the importance of adherence to the drug regimen. Familial or social issues that impede adherence may need to be addressed before adherence can be improved. Issues to be addressed include financial or housing insecurity, concomitant mental health problems, need for substance abuse treatment, and fear of HIV disclosure. In some situations, clinicians may need to involve outside agencies, such as child protective services, to ensure support of a child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting a child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and the 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; however, durability of adherence improvement is variable after DOT is discontinued.[9]

Pharmacokinetic Factors

Treatment failure can result from inadequate drug exposure as well as poor adherence.[10] Children consistently require higher weight-based dosing of ARV drugs than do adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range.[11] Causes of subtherapeutic drug levels may include failure to increase dosing to accommodate for a child's rapid growth or impaired absorption because of gastrointestinal symptoms such as vomiting or diarrhea. Because drug exposure can be enhanced or reduced by administering medications with food, a clinician should review the food/fasting requirements of a regimen with both patient and caregiver. Drug interactions can alter drug metabolism; therefore, 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 studies suggest that genetic polymorphisms may influence PK and therapeutic response for a number of antiretroviral (ARV) medications.[12-14] 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 (See Antiretroviral Drug-Resistance Testing)

ARV drug resistance may develop in children who are taking ARV drugs in the context of inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs in the current regimen, it is unlikely that the child is currently taking these medications. The presence of mutations that confer resistance to one or more drugs in the regimen is consistent with patient adherence (partial or full) to the regimen at that time, but failure of the regimen to adequately suppress viral replication because of drug resistance. Because virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays in the absence of the selective pressure of ARV drugs, ARV resistance testing should be performed while a patient is still taking the failing regimen or within 4 weeks of discontinuing the regimen. Resistance testing can be used to assess reasons for current virologic failure and to identify active ARV medications for future regimens. (See Antiretroviral Drug-Resistance Testing.)

Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Non-Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Obtain description of: • *WHO* gives medications • *WHEN* medications are taken/given • *WHAT* medications are taken/given (names, doses) • *WHERE* medications are kept/ administered • Have open-ended discussion of experiences taking/giving medications and barriers/challenges	• Identify or re-engage family members to support/supervise adherence • Establish fixed daily times and routines for medication administration • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are co-formulated under a third or fourth name. • Explore opportunities for facility or home-based DOT
	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 • Observe administration/tolerance • Monitor treatment response	• Simplify medication regimen, if feasible • Substitute new agents if single ARV is poorly tolerated • Consider gastric tube placement to facilitate adherence • Consider DOT • Use tools to simplify administration (e.g., pill boxes, reminders [including alarms], integrated medication packaging for AM or PM dosing) • Suggest relaxation techniques
	4. Conduct psychosocial assessment • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes: • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child's achievement level • Substance abuse (child, caretaker, family members) • Mental health and behavior • Child/youth and caretaker beliefs about cART • Disclosure status (to child and others)	• 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 protective services and alternate care settings when necessary

Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Pharmaco-kinetics and Dosing Issues	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 ARV drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	• Adjust drug doses • Discontinue or substitute competing medications • Reinforce applicable food restrictions
ARV Drug Resistance	1. Perform resistance testing, as appropriate (see Antiretroviral Drug- Resistance Testing).	• If minimal or no resistance detected to current drugs, focus on improving adherence • If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see Approach to the Management of Virologic Failure of Antiretroviral Treatment).

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, DOT = directly observed therapy

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Approach to the Management of Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- The causes of virologic treatment failure, which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions, should be assessed and addressed **(AII)**.
- When deciding how to treat a child with virologic treatment failure, the probability of achieving durable virologic suppression should be considered, as well as the future options for treatment, should durable suppression not be achieved **(AII)**.
- Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

General

Note: This section will focus only on the management of virologic treatment failure. For patients with immunologic failure or clinical failure in the setting of virologic suppression, non-HIV-related causes of immunologic or clinical failure should be identified and addressed, though frequently no specific etiology is identified. There is no consensus about the best management of immunologic or clinical failure in the setting of sustained virologic suppression.

Once the potential causes of virologic treatment failure have been identified and addressed, the child should be assessed to determine whether a change in antiretroviral (ARV) drug regimen is necessary and advisable. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The urgency of implementing a more effective treatment regimen depends on a child's immunologic status, with the greatest urgency in 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 a child's virus, and the likelihood of adherence to the new regimen. If poor adherence has been a major contributor to virologic treatment failure, and factors contributing to poor adherence have not been adequately addressed, changing the ARV drug regimen may not be advisable because it is not likely to result in virologic suppression and is likely to promote accumulation of additional drug resistance mutations.

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 a child's clinical and immunologic status. For example, for older children or adolescents with severe immunosuppression (such as CD4 T lymphocyte [CD4 cell] counts <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 is likely at less risk of clinical disease progression in the short term, so an immediate change in therapy is less urgent. However, continued treatment of a child with persistently detectable viremia increases the risk of immunologic decline or clinical disease progression and leads to further accumulation of resistance mutations, possibly further limiting future treatment options.[2, 3] Finally, even in children with advanced clinical and/or immunologic status, initiating a new regimen in the face of persistent adherence difficulties is unlikely to result in virologic suppression, and it is likely to promote accumulation of additional resistance.

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

When deciding whether to change a child's ARV drug regimen, a clinician must assess the likelihood that the new regimen will 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 and adolescents. 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.[4] It is important that the clinician alert the patient to potential toxicities and discuss strategies to minimize their impact. The likelihood of adherence to a new regimen plays a significant role in determining whether to change an ARV 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,[5] psychosocial stressors,[6, 7] health beliefs,[8] and prior adherence to medication (see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents for more detail). Importantly, adherence to combination antiretroviral therapy (cART) may change rapidly and unexpectedly with a change in family circumstances or as a child moves through progressive developmental stages. Thus, a clinician may choose to target a new ARV regimen to start at a time when a child and his or her family are most likely to adhere to the new regimen for a sustained period.

Categories of Children with Treatment Failure and Approaches to Consider

No Viral Drug Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications suggests that the virus is not being exposed to the ARV agents. This lack of ARV drug exposure is usually a result of 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 ensured, then adherence to the current regimen should result in undetectable plasma levels. Resistance testing should take place while a child is on therapy. After discontinuation of therapy, predominant plasma viral strains may quickly revert to wild-type and re-emerge as the predominant viral population, in which case resistance testing may fail to reveal drug-resistant virus (see Antiretroviral Drug-Resistance Testing). Thus, if a child on cART 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 identifying resistance in this situation is to restart the prior medications while emphasizing adherence and repeat resistance testing in 4 weeks if plasma virus remains detectable. If plasma virus is undetectable with the most sensitive assays, the virus is likely to be susceptible to the current therapy.

Viral Resistance to Current Antiretroviral Therapy

The recommendation in this situation is to start a new cART regimen in order to fully suppress and sustain plasma viral load below the limits of detection and prevent 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), ART history, availability of new drugs and classes of agents, and consideration of potential toxicities. Some ARV drugs (such as nucleoside reverse transcriptase inhibitors [NRTIs]) may contribute partial ARV activity to an ARV 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 ensure that the replacement drug will be fully active. This is particularly true for the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz, for which cross-resistance with drug mutations is uniformly seen.

The availability of an increasing number of ARV drugs, including some with new viral targets, makes complete virologic suppression achievable for many patients with treatment failure. Unfortunately, the lack of pediatric formulations and dosing information for some of these agents limits the number of options available for younger 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 difficulties contributing to poor adherence with the current regimen are likely to continue, emphasis and effort should be placed on improving adherence before initiating a new regimen (see next section).

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

In 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 maintaining HIV viral load at <10,000 to 20,000 copies/mL may offer ongoing immunologic and clinical benefit;[9, 10] pediatric studies suggest that children receiving cART with viral load <1,000 to 5,000 copies/mL may not achieve significantly better clinical and immunologic outcomes by changing therapy.[3, 4, 11] Several cohort studies show a clinical benefit of remaining on cART, regardless of whether it leads to a decrease in viral load. The principal risk associated with continuing a failing regimen when no suppressive regimen is available is the development of additional resistance mutations that can limit future treatment options. This risk is especially true for NNRTI-containing regimens but also occurs with prolonged use of non-suppressive protease inhibitor-containing regimens.[2, 4, 12]

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 minimizing risk of drug toxicity and development of new resistance mutations to multiple classes of drugs. Simplified (often all-NRTI) "holding regimens" are sometimes used in place of continuing a failing cART regimen (see Choice of Therapy When Two Agents Cannot be Identified). 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, 13-21] This approach should be regarded as acceptable but not ideal; these patients should be followed more closely than those with stable virologic status and the potential for successful initiation of a fully suppressive ARV drug regimen should be reassessed at every opportunity. Interrupting therapy completely will avoid new drug resistance, but potentially at higher risk of immunologic or clinical progression (see Treatment Interruption).

When managing disease progression in patients with advanced disease and extensive resistance, quality of life must be considered. The relative benefits (e.g., reduced viral fitness, continued clinical benefit despite resistance) and burdens of continuing a failing ARV drug regimen should be discussed. Decisions to continue, discontinue, or simplify cART should be made collaboratively with patients, families, and clinicians and should be consistent with the patients' or families' stated values and goals for care.

Children with Ongoing Adherence Problems as a Major Reason for Virologic Treatment Failure

If there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen is unlikely, emphasis and effort should be placed on improving adherence before initiating a new regimen (see Adherence). Adherence in infants and younger children depends completely on their caregivers. When other intensive measures to address adherence problems have failed and caretakers appear unable or unwilling to administer medications, child protective services may need to be requested to assess the need for additional support for current caretakers or for a change in caretaker. When efforts to improve adherence will require several weeks or months, some clinicians may choose to continue the current non-suppressive regimen or use a simplified, NRTI-only, non-suppressive regimen that may provide some clinical and immunologic benefit while preserving future ARV drug choices (see Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered).[13, 22, 23] Treatment with non-suppressive regimens in such situations should be regarded as an acceptable but not ideal interim strategy to prevent immunologic and clinical deterioration while working on adherence. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV drug regimen should be reassessed at every opportunity.

Complete treatment interruption for a persistently nonadherent patient should prevent accumulation of additional drug resistance but has been associated with immunologic declines and poor clinical outcomes.[24] However, the strategy of complete treatment interruption has not been fully evaluated in children. Although complete treatment interruption is not recommended for cases of ongoing poor adherence, it is recognized that some patients may decide on their own to stop all medications. Although careful monitoring and open communication between provider and patient are always important, they are especially critical in these situations (see Treatment Interruption).

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Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Antiretroviral (ARV) regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*)**.
- The new regimen should include at least two, but preferably three, fully active ARV medications with assessment of anticipated ARV 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)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

General

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least two, but preferably three, fully active antiretroviral (ARV) agents from at least two different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.[1-5] This often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen should not be done because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency because of the presence of drug-resistance mutations that confer cross resistance within a drug class. In children who are changing therapy owing to the occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher concentrations in the central nervous system.[6-10]

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with a patient in an age- and development-appropriate manner and with a patient's caregivers. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate administration of a regimen. Timing of medication administration is particularly important to ensure adequate ARV drug exposures throughout the day. Palatability, size and number of pills, and dosing frequency all need to be considered when choosing a new regimen.[11]

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. ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in Table 20, 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 a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, a change to a protease inhibitor (PI)-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 (see below). If a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is generally recommended. Lopinavir/ritonavir-based regimens have also been shown to have durable ARV activity in some PI-experienced children.[12-14] Choice of the new dual-nucleoside reverse transcriptase inhibitor (NRTI) component is particularly important when constructing a regimen because the choice of an insufficiently potent NRTI may result in selection of additional NRTI-related drug-resistance 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).

The availability of new drugs in existing classes (e.g., the NNRTI etravirine) and new classes of drugs (e.g., integrase inhibitors) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (Table 20). In studies of adults, etravirine retains activity against nevirapine- or efavirenz-resistant viruses when used in a regimen that also contains darunavir/ritonavir and if the number of NNRTI resistance-associated mutations is limited.[15, 16] Etravirine in combination with ritonavir-boosted darunavir, as part of a new combination antiretroviral therapy (cART) regimen, has been shown to be a safe and effective option for children in whom cART fails.[17, 18] Etravirine is approved for use in children aged ≥6 years;[17, 19] studies in younger children are under way. Studies of treatment-experienced adult and adolescent patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), often coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced patients with multidrug-resistant virus, is associated with good virologic responses.[20-23] Raltegravir, in combination with optimized background therapy, was safe and effective in treatment-experienced children aged 2 to 16 years,[24] for whom it is Food and Drug Administration (FDA)-approved. Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States.[25] It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. Appendix A: 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 ARV drugs, including new drugs in existing classes such as darunavir and agents in new classes of drugs such as CCR5 antagonists (e.g., maraviroc, approved for use in adolescents aged ≥16 years) and integrase inhibitors (e.g., raltegravir, approved for use in children aged ≥2 years [FDA, December 21, 2011]).

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (such as by switching from a liquid to pill formulation or to a new formulation [such as ritonavir tablet]). 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.[26-28] The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified and ideally is 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 is approved for use in heavily treatment-experienced patients based on potent ARV activity in heavily treatment-experienced adults; it has been approved for use in children aged ≥6 years.[29, 30] Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children aged ≥6 years.[31, 32] Enfuvirtide must be administered by subcutaneous injection twice daily, a disadvantage that presents a greater challenge to adherence in adolescents than in younger children. Enfuvirtide can be considered an option when designing a new regimen for children in whom multiple classes of ARV medications have failed, but newer and better tolerated agents have largely supplanted use of enfuvirtide.

Pharmacokinetic (PK) studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in adults[33-35] and in children.[36-38] PK studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs.[39, 40] A study in Thailand of 50 PI-naive 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 1000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks in ≥50% of patients. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series;[41] however, multidrug regimens should be used cautiously because of their complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring 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 because of the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may lessen the need for dual-PI regimens.

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians 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.

Therapeutic Options When Two Fully Active Agents Cannot Be Identified or Administered

It may be impossible to provide an effective and sustainable therapeutic regimen because no combination of currently available agents is active against extensive drug-resistant virus in a patient or because a patient is unable to adhere to or tolerate cART.

In such cases, non-suppressive regimens (or holding regimens) are sometimes used pending availability of additional active, tolerable drugs or improvement in ability to adhere. This interim strategy allows for the overall objective of preventing clinical and immunological deterioration until new agents are available to design a regimen that can be expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive cART regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, patients can derive immunologic and clinical benefit despite persistent viremia from treatment with lamivudine monotherapy or with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir.[42, 43]

The newer NNRTI etravirine retains activity against many nevirapine- or efavirenz-resistant viruses with a limited number of NNRTI resistance-associated mutations. Ongoing use of efavirenz or nevirapine as part of a failing regimen should be avoided because it may lead to accumulation of additional NNRTI resistance

mutations that will reduce etravirine activity and preclude its use in a future, suppressive regimen,[44] and it may allow for accumulation of additional NRTI resistance.[45]

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.[46-49] However, continued PI use in the presence of resistance may limit viral replication and be beneficial to some patients.

When clinical or immunologic deterioration occurs while patients are receiving such holding regimens, it is important to re-assess patient readiness and regimen availability. It may be appropriate to use investigational agents or agents approved for older age groups as second fully active drugs in the new regimen (see The Use of Antiretroviral Agents Not Approved for Use in Children). In general, a single, new, fully active agent should not be added to non-suppressive holding regimens because resistance is likely to develop quickly.

Table 20. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients With Failed Antiretroviral Therapy and Evidence of Viral Resistance[a]

Prior Regimen	Recommended Change (in order of relative preference)[a]
2 NRTIs + NNRTI	• 2 NRTIs + PI • 2 NRTI + integrase inhibitor[b]
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + alternative RTV-boosted PI • 2 NRTIs + integrase inhibitor[b] • NRTI(s) + integrase inhibitor + (NNRTI *or* alternative RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor[b] • Integrase inhibitor[b] + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed regimen(s) that included NRTI(s), NNRTI(s), and PI(s)	• > 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor[b] (consider adding T-20 and/or MVC,[c] if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,[c] T-20, or integrase inhibitor,[b] if additional active drug[s] needed) • > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor[b] if additional active drug[s] needed)

[a] ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly 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. *Please see individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance.* Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are listed in relative order of preference and are provided as examples but the list is not exhaustive.

[b] Caution advised when using raltegravir in children aged ≤6 years because pharmacokinetic and efficacy data are particularly limited in this age group.

[c] No current FDA-approved pediatric indication for maraviroc.

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

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The Use of Antiretroviral Agents Not Approved for Use In Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age because many of the recently approved, more convenient, and potent agents are approved for use in adults before pharmacokinetic (PK), safety, and efficacy data are available in children **(AII)**.
- Dosing in a child of ARVs only approved for adults cannot simply be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Such use of ARVs should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and PKs of ARVs that are not yet Food and Drug Administration (FDA)-approved for children **(AI*)**.
- Whenever possible, use of ARVs 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)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

It has long been the practice of physicians, especially pediatricians, to prescribe medications in off-label situations, meaning for indications or populations that do not fall within the official, Food and Drug Administration (FDA)-approved indication.[1] The relatively small market for pediatric antiretroviral (ARV) drugs and few children available to participate in clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some ARV drugs at the same time their use in adults is approved. Pediatric HIV specialists may need to prescribe these agents because drugs currently available for pediatric use afford few options for heavily treated children and adolescents with high levels of resistance and because the newer agents offer improvements in tolerability and ease of adherence with less frequent dosing.

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

Another major factor leading to off-label use of ARVs 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 treatment with multiple non-suppressive regimens. Cross resistance between fully approved ARVs within a class makes it difficult to find a combination of agents likely to fully suppress the virus. In an effort to create a regimen likely to achieve complete virologic suppression in an individual patient, providers must identify 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 use of agents not yet approved for pediatric use causes some difficulties. One of the major issues is lack of data on appropriate dosing in children. Agents are approved for adult use before being approved for pediatric use because safety and pharmacokinetic (PK) studies in children have not yet been completed. Sometimes studies in children are ongoing and some data are available, but other times, pediatric 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 ARV use. To date, no ARV has been found to have adverse effects that preclude use uniquely in children, but until an agent has been tested in children, it cannot be considered to be free of such an effect. In addition, adverse effects noted in adults may be of more substantial concern in a growing and developing child.

Difficulties in pediatric dosing for off-label use of ARV drugs are even more problematic than the potential for adverse effects. 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 PKs. In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[3]

In summary, use of ARV agents without a pediatric indication is an absolute necessity for treatment of some HIV-infected children, but such off-label use must be done with care. **It is essential that a 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.**

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Role of Therapeutic Drug Monitoring in Management of Treatment Failure (Last updated August 11, 2011; last reviewed November 1, 2012)

Therapeutic drug monitoring (TDM) is 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 combination antiretroviral therapy because:[1, 2]

- Interpatient variability in antiretroviral (ARV) exposure (i.e., plasma drug concentrations) using standard recommended doses is high;
- 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 ARV exposure in pediatric patients than in adults.[3] Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated ARV drug dose. Even when using dose recommendations from published pediatric guidelines, children often receive inadequate ARV doses.[4]

There are two main situations in which TDM may 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 drug dosage when changing to a new regimen in a patient whose virus has reduced susceptibility to that drug.

For TDM to be useful, the relationship between ARV drug concentrations and anti-HIV effects must be clearly defined.[5-7] This association is strongest with protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs),[8] but maintaining adequate nucleoside reverse transcriptase inhibitor (NRTI) serum concentrations also has been shown to be important for maximal anti-HIV activity.[9] The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents.[7] 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 ARV drugs.[10]

Table 21 presents recommendations for the minimum target trough concentrations of PIs and NNRTIs in patients without evidence of resistance to those drugs. In ARV-experienced patients, the choice of minimum target trough concentration should be based on results of resistance testing.[11-13] 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.[8, 14-18] Clinicians should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

TDM is not recommended for routine use but may be considered potentially useful for patients:

- In whom clinical response is different from that expected;
- Who are treatment experienced and 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;
- Who may experience potential difficulties with drug administration related to suboptimal dietary intake or malabsorption, incorrect dosing or caregiver measuring errors, or concerns surrounding adherence; and
- Who experience drug or food interactions, including interactions resulting from alteration of drug formulations by crushing medications or mixing them with various foods and liquids.

Current limitations for pediatric ARV TDM include:

- Prolonged time for laboratory processing in the face of potentially diminishing benefit the longer a patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times, which make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results;[19, 20]
- Single trough measurements within the target range, which 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[a]

Drug	Concentration (ng/mL)
Atazanavir	150
Fosamprenavir	400 (measured as amprenavir concentration)
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

[a] Reprinted from: *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

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Discontinuation or Interruption of Therapy (Last updated November 1, 2012; last reviewed November 1, 2012)

General

Discontinuation of combination antiretroviral therapy (cART) 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. Observational studies of children and youth with unplanned or non-prescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy.[1-3] Although events precipitating ART interruptions are usually unplanned, planned discontinuation of therapy was considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with ART. While one trial of children randomized to structured treatment interruptions (STI) with CD4-guided resumption of cART reported no serious clinical outcomes,[4] adult trials have demonstrated significantly higher morbidity and mortality in adults randomized to STI compared with continuous cART.[5] Long-term STI as a drug-sparing strategy or to give patients "drug holidays" is not recommended for children or adults outside of a clinical trial. The discussion below provides more detailed guidance for interruption of cART and the risks and benefits in specific situations.

Short-Term Therapy Interruption

In children, 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. A 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; however, when possible, patients should be allowed to continue regular cART with minimal fluid intake. For a prolonged period of restricted oral intake, all drugs in an ARV regimen should be stopped at the same time if the medications have similar half-lives. In the case of serious or life-threatening ARV drug toxicity, all drugs should be stopped immediately.

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation.[6-9] As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase risk of selection of non-nucleoside reverse transcriptase inhibitors (NNRTI)-resistant mutations. Certain genetic polymorphisms that are more common in certain racial and ethnic groups (i.e., African Americans, Hispanics) may result in a slower rate of drug clearance.[8, 9] To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other ARV drugs (NRTI backbone or protease inhibitor [PI]) for a period of time.[7] An alternative is to substitute a PI for the NNRTI up to 4 weeks before interrupting all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective strategy, but information in children is unavailable and, because the PKs of these agents are different in children, the recommendations for adults may not be applicable.[10-12]

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 used 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.[10] In cases where nevirapine has been discontinued for more than 2 weeks, another 2-week dose escalation is recommended when the drug is reintroduced.

Long-Term Structured Treatment Interruptions

Strategies for STI for long periods of time traditionally have been proposed with the aim of reducing toxicities and costs associated with long-term cART.

In adults, two large, randomized clinical trials have demonstrated increased morbidity when CD4 T lymphocyte (CD4 cell) count was used as an indication to stop and start therapy. The Strategies for Management of Antiretroviral Therapy (SMART) trial stopped cART when the CD4 cell count was >350 cells/mm^3 and reintroduced therapy when the count was <250 cells/mm^3. Compared with the group receiving continuous cART, the STI group had an increased risk of disease progression and death.[5] Interruption of cART was also associated with elevations in biomarkers of inflammation that were predictive of morbidity and mortality independent of CD4 cell count.[13] Similarly, in the TRIVICAN trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior.[14] Studies in adults using a CD4 cell count <350 cells/mm^3 as a trigger to restart therapy did not report significant differences in serious disease progression or death.[15, 16] However, another large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy.[17] In light of these data, the current Department of Health and Human Services guidelines for adults recommend against planned long-term STI in adults (see *Adult and Adolescent Treatment Guidelines*).

In children, there have been fewer studies of long-term STI. In one study, children with controlled viral load (HIV RNA <400 copies/mL for >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.[18] However, new drug-resistance mutations were detected in 3 of 14 children in the STI study. In the European (PENTA) trial, 109 children with virologic suppression on cART were randomized to continuous therapy (CT) versus treatment interruption with CD4-guided re-initiation of cART. On average, CD4 values decreased sharply in the first 10 weeks after STI. However, most children in the STI arm (almost 60%) did not reach CD4 criteria to restart therapy over 48 weeks. Children in the STI arm spent significantly less time on cART than children in the CT arm.[4] None of the children in the trial experienced serious clinical illnesses or events, and the appearance of new drug-resistance mutations did not differ between the two arms.[4]

In some populations of children, STI has been more specifically considered. In the United States and other developed countries, most HIV-infected children begin cART during infancy.[19, 20] Many of them have had controlled viral replication for many years and are growing and developing normally. One trial was designed to answer whether infants who initiated cART early could safely discontinue therapy at some point and reinitiate treatment based on CD4 cell decline. The CHER study in South Africa assessed outcomes in infants randomized to deferred cART (initiation driven by CDC stage and CD4 status), immediate cART with interruption after 40 weeks, or immediate cART with interruption after 96 weeks.[21, 22] While the two arms of interrupted therapy led to better outcomes compared to the deferred arms, up to 80% of infants had to restart therapy by the end of follow-up. The long-term outcomes in children after this interruption remain unknown and it is unclear if the short period of time on cART saved by most children merits the potential risks associated with cessation. Another scenario often raised involves patients who have limited treatment options and who cannot achieve an undetectable viral load despite aggressive cART. In such cases, continuation of non-suppressive therapy is recommended because, despite detectable viral replication, immunologic benefit has been well documented.[23-26]

Given the increased availability of medications with less toxicity, the potential benefits of long-term STI may be decreasing. Current data do not support use of long-term STI in clinical care of HIV-infected children.

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Antiretroviral Drug-Resistance Testing (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Antiretroviral (ARV) drug-resistance testing is recommended before initiation of therapy in all treatment-naive children **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
- ARV drug resistance testing is recommended before changing therapy because of treatment failure **(AI*)**.
- Resistance testing in patients with virological failure should be done while they are still on the failing regimen or within 4 weeks of discontinuation **(AII*)**.
- Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ARV therapy regimens **(BIII)**.
- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful. Consequently, previously used ARV agents and previous resistance test results 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 ARV regimen in pediatric patients **(AI*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated 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 outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

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

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 (ART) 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. Unfortunately, mutations in HIV RNA readily arise during viral quantification because HIV reverse transcriptase (RT) is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral (ARV) 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 ARV agents. Viral coreceptor (tropism) assays have been successfully used to detect virus with tropism that will (CCR5 tropism) or will not (CXCR4 or mixed tropism) be blocked by CCR5 antagonists. Both genotypic assays and phenotypic assays currently

are used to detect the presence of virus that is resistant to inhibitors of the HIV RT, integrase (IN), or protease (PR). Clinical experience with testing for viral resistance to other agents is more limited, but genotypic assays that assess mutations in gp41 (envelope) genes also are commercially available. 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 and PR inhibitors and integrase strand transfer inhibitors (INSTIs) are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and IN 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 generally are available within 1 to 2 weeks of sample collection.[2] Interpretation of test results requires knowledge of the mutations selected by different ARV drugs and of the potential for cross resistance to other drugs conferred by certain mutations. For some drugs, the genetic barrier to the development of resistance is low, and a single nucleotide mutation is enough to confer high-level resistance sufficient to remove any clinical utility of the drug. This is exemplified by resistance to nevirapine resulting from mutations in the HIV RT. Other mutations lead to drug resistance but simultaneously impair HIV replication. Clinically useful activity of the ARV 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 RT mutation.[3] By contrast, HIV evolution to high-level resistance to some drugs is associated with the emergence of mutations that confer the resistance as well as compensatory mutations that allow the virus to replicate more efficiently in the presence of the ARV agent.

The International AIDS Society-USA (IAS-USA) and the Stanford University HIV Drug Resistance Database maintain lists of significant resistance-associated mutations relevant to currently available ARV drugs (see http://www.iasusa.org/resistance_mutations, 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 ART 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 on viral replication of mutations that are present among an individual's HIV variants. As they are most often performed, phenotypic assays involve PCR amplification of the RT, IN, PR, or gp41 envelope gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a cloned strain of HIV that expresses a reporter gene. Replication of this recombinant virus in the presence of a range of drug concentrations is monitored by quantification of the reporter gene and is compared with replication of a reference drug susceptible HIV variant. The drug concentration that inhibits viral replication by 50% (that is, the mean inhibitory concentration, or IC_{50}) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance change). Automated, recombinant phenotypic assays that can produce results in 2 to 3 weeks are commercially available; however, they are more costly than genotypic assays.

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 RT, IN, and PR 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. Therefore, the sample is assigned a predicted phenotype susceptibility (or "virtual phenotype") based on the data from specimens matching the patient's genotype. The primary limitations of this approach are that its predictive power depends upon the sensitivity of the genotypic methods used and the number of matches to the patient's genotype.

Tropism (Viral Coreceptor Usage) Assays

HIV enters cells by a complex, multistep process that involves sequential interactions between the HIV envelope protein molecules and the CD4 receptor, and then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses initially are CCR5 tropic in the majority of untreated individuals, including infants and children infected by mother-to-child transmission (MTCT) of HIV. 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). ARV-treated patients with extensive drug resistance are more likely to harbor detectable CXCR4- or D/M-tropic virus than untreated patients with comparable CD4 T lymphocyte (CD4 cell) counts.[11]

Resistance to CCR5 antagonists is detected using specialized phenotypic assay methods (Phenoscript [VIRalliance] 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.

Any indication of CXCR4 usage by virus detected in a patient is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor use assays should be performed before a CCR5 inhibitor is used and should be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc.

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 CXCR4-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 CXCR4- or D/M-tropic virus in patients initiating a CCR5 inhibitor-based regimen. The current version of the Trofile assay has improved sensitivity and is able to detect CXCR4- or D/M-tropic virus representing as little as 0.3% of the plasma virus.[12, 13]

One of the tropism assays also can be performed following amplification of HIV sequences from peripheral blood DNA (Trofile-DNA [Monogram Biosciences, Inc.]) and may be useful when a change to a regimen containing a CCR5 antagonist is being considered for an individual with an undetectable plasma viral load.

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 variants are likely to exist at low levels in every HIV-infected patient. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population or are present in the reservoir of latently infected cells may not be detected by any of the currently available commercial resistance assays.[14] Consequently, a review of the past use of ARV agents is important in making decisions regarding the choice of new agents for patients with virologic failure.

Genotypic assays have been proposed as an alternative approach to detemining the tropism of plasma HIV. However, they are not currently recommended because the limited experience with this approach indicates that the sensitivity and specificity are lower than phenotypic tropism assays.[15]

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 to 6 weeks after ARV drugs are stopped.[16-18] As a result, resistance testing is of greatest value when performed 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,[19] 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 Management of Treatment-Experienced Infants, Children, and Adolescents).

Use of Resistance Assays in Determining Initial Treatment

MTCT transmission and behavioral transmission of drug-resistant HIV strains have been well documented and are associated with suboptimal virologic response to initial ART.[20-24] Drug-resistant variants of HIV may persist for months after birth in infected infants[25] and impair the response to ART.[26] Consequently, ARV drug-resistance testing is recommended for all treatment-naive children before therapy is initiated. Genotypic testing is preferred in this setting because it may reveal the presence of both resistance mutations and polymorphisms that facilitate the replication of drug-resistant virus.

Use of Resistance Assays in the Event of Virologic Failure

Several studies in adults[2, 4-10] have indicated 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,[27] resistance testing appears to be a useful tool in selecting active drugs when changing ARV 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 ART 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 (see Management of Treatment-Experienced Infants, Children, and Adolescents).

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Conclusion (Last updated August 11, 2011; last reviewed November 1, 2012)

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral (ARV) 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 ARV 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 (CDC), the National Institutes of Health (NIH), the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Disease Society (PIDS), and the American Academy of Pediatrics (AAP) 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 website.[2]

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Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Stavudine (d4T, Zerit)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

Abacavir (ABC, Ziagen) (Last updated August 11, 2011; last reviewed November 1, 2012)

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

Dosing Recommendations

Neonate/infant dose:

- Not approved for infants aged <3 months.

Pediatric dose:

- *Oral solution (≥3 months of age):*
  8 mg/kg (maximum 300 mg) twice daily.

  In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte count, can consider using once-daily abacavir dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see text).

Scored 300 mg tablet (weight ≥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 (aged ≥16 years)/adult dose:

- 300 mg twice daily or 600 mg once daily.

Trizivir

- *Adolescent (weight ≥40 kg)/adult dose:*
  One tablet twice 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

- Test patients for the HLA-B*5701 allele before 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.
- ABC can be given without regard to food.
- Caution patients and parents about risk of serious HSR that can be fatal. Do not re-challenge.

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 creatinine clearance (CrCl) <50 mL/min,

Epzicom

- *Adolescent (≥16 years of age)/adult dose:* One tablet once daily.

patients on dialysis, or those 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 P (CYP) 450 enzymes. Thus, it should not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors.
- Abacavir is metabolized by alcohol dehydrogenase and glucuronyl transferase. 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 (HSRs) 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 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 an HSR is suspected, abacavir should be stopped and **not restarted because hypotension and death have occurred upon re-challenge**. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis can 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 Antiviral 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 Use: Abacavir is Food and Drug Administration (FDA) approved for use in HIV-infected children as one of the drugs for part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The liquid formulation of abacavir is more palatable than zidovudine; it has less of an effect on mitochondrial function than zidovudine, stavudine, or didanosine; and it has more durable antiviral effectiveness in pediatric trials.[1, 2] The risk of abacavir hypersensitivity syndrome, the major toxicity limiting abacavir's use, is greatly reduced by testing patients for HLA-B*5701 and by not using abacavir in those who test positive for the HLA-B*5701 allele.

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that children

have more rapid clearance of abacavir than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure.[3, 4] Metabolic clearance of abacavir in adolescents and young adults (ages 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.[5]

Plasma area under the drug concentration by time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.[6, 7] Intracellular concentrations of NRTIs are most strongly associated with antiviral effectiveness, and the active form of abacavir is the intracellular metabolite carbovir triphosphate.[8, 9] Measurement of intracellular carbovir triphosphate is more difficult than measurement of plasma AUC, so the abacavir plasma AUC is often taken as a proxy measurement for intracellular concentrations. However, this relationship is not sufficiently strong that changes in plasma AUC can be assumed to reflect true changes in intracellular active drug. For example, although overall intracellular carbovir triphosphate was correlated with abacavir plasma AUC, this relationship was not found when gender was considered in PK modeling[10] because carbovir triphosphate concentrations were higher in females than in males.[10-12] This effect of gender on intracellular triphosphates has also been found with zidovudine and lamivudine.[8, 13]

In studies in adults, abacavir plasma AUC is decreased 17% by concurrent use of atazanavir/ritonavir and decreased 32% by concurrent use of lopinavir/ritonavir.[14] In a study comparing PK parameters of abacavir in combination with either lopinavir/ritonavir or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of lopinavir/ritonavir, but the carbovir triphosphate concentration seemed to increase in the lopinavir/ritonavir group.[12]

These effects of gender and concurrent PI use add to the complexity of linking readily available plasma abacavir AUC with more difficult to obtain but pharmacodynamically more important intracellular carbovir triphosphate concentrations. These effects also need to be kept in mind when considering data supporting the use of once-daily abacavir in children (presented **in the table below**).

Abacavir 600 mg once daily is standard for use in adults, but once-daily use for children is still controversial. The PENTA-13 crossover trial studied abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in 24 children aged 2 to 13 years who had undetectable or low, stable viral loads at the time of changing from twice-daily to once-daily abacavir. This study showed equivalent $AUC_{0\text{-}24}$ for both drugs and improved acceptability in the once-daily dosing arm.[15, 16] However, trough concentrations were lower in younger children (aged 2–6 years) receiving the once-daily regimen.[16] The PENTA-15 crossover trial studied 18 children aged 3 to 36 months, again comparing abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in children with viral loads <400 copies/mL or "stable" on twice-daily abacavir at baseline. $AUC_{0\text{-}24}$ and clearance were similar on the once- and twice-daily regimens. After the change from twice-daily to once-daily abacavir, viral load remained <400 copies/mL in 16 of 18 participants through 48 weeks of monitoring.[17] A study of 41 children aged 3 to 6 years (median age 7.6 years) in Uganda who were stable on twice-daily abacavir also showed equivalent $AUC_{0\text{-}24}$ and good clinical outcome (disease stage and CD4 T lymphocyte (CD4 cell) count) after the switch to once-daily abacavir, with median follow-up of 1.15 years. Viral load testing was not done.[18]

Abacavir Steady State Pharmacokinetics When Dosed Once Daily or Twice Daily

Study/ (reference)	PENTA 15[17]		PENTA 13[16]		Arrow[18]		5		10	
Location	Europe		Europe		Uganda		U.S.		U.S.	
N	18		14		36		15	15	27	
Age (years)	2		5		7		16[a]	22[a]	45[a]	
Sex (% male)	56%		43%		42%		53%	53%	70%	
Race (% black or African American)	78%				100%		53%	60%	18%	
Body weight (kg)	11		19		19		63[a]	72[a]	NA	
Concurrent PI use	8		1		0		9	0	NA	
Dosing interval (hours)	12	24	12	24	12	24	12	12	12	24
Administered dose median (mg/kg) or fixed amount (mg)	8.04	16.02	8.1	16.4	19.6[c]	19.1	300[d]	300[d]	300[d]	600[d]
Administered dose range (mg/kg)	7.7-8.3[e]	15.5-16.3[e]	5.0-8.4	15.6-17.1	15.4-23.1[c]	14.6-23.1				
AUC_{0-24} (mg*hr/L)	10.85[b]	11.57[b]	9.91[b]	13.37[b]	15.6[b]	15.28[b]	7.01	6.59	7.90[b]	8.52[b]
C_{max} (mg/L)	1.38[b]	4.68[b]	2.14[b]	4.80[b]	4.18[b]	6.84[b]	2.58	2.74	1.84[b]	3.85[b]
C_{min} (mg/L)	0.03[b]	<0.015[b]	0.025[b]	<0.015[b]	0.021[b]	0.006[b]				
Cl/F/kg (L/hr/kg)	1.47[b]	1.38[b]	1.58[b]	1.16[b]	1.23[b]	1.24[b]	9.80[f]	12.10[f]		
Carbovir-triphosphate AUC_{0-24}(h*fmol/10^6 cells)							530[g]	315[g]	814	1,051

Key to Abbreviations: AUC = area under the curve, PI = protease inhibitor

Data are medians except as noted.

[a] mean
[b] geometric mean
[c] total daily dose in mg/kg (divided doses were given but sometimes in unequal amounts morning and evening)
[d] total dose in mg
[e] interquartile range
[f] clearance in mL/min/kg
[g] AUC in fmol/10^6 cells

No clinical trials exist involving children who initiated ART with once-daily dosing of abacavir. All three pediatric studies described in the table above enrolled only patients who had low viral loads or were "clinically stable" on twice-daily abacavir before changing to once-daily dosing. Therefore, the Panel suggests that in clinically stable patients with undetectable viral loads and stable CD4 cell counts, switching to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose to maximum of 600 mg once daily) can be considered.

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Didanosine (ddI, Videx) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Videx pediatric powder for oral solution: reconstituted 10 mg/mL

Videx enteric-coated (EC) delayed-release capsules (EC 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 (aged 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 pharmacokinetic 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 (aged ≥3 months to 8 months):

- 100 mg/m^2 of body surface area every 12 hours.

Pediatric dose of oral solution (age >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; maximum dose 200 mg/dose twice daily.)

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

Body Weight (kg)	Dose (mg)
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-naive children aged 3–21 years, 240 mg/m^2 of body surface area once daily (oral solution or capsules) has been used with effective viral suppression.

Selected Adverse Events

- Peripheral neuropathy
- Electrolyte abnormalities
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in adults. (The risk is increased when ddI is used in combination with stavudine [d4T].)
- Pancreatitis (less common in children than in adults, more common in adults when ddI is used in combination with tenofovir [TDF] or d4T)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddI, administration of ddI on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer ddI without regard to timing of meals (see text below).
- ddI oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual protease inhibitor for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of ddI, than for the enteric coated formulation.

Adolescent/adult dose:

Body Weight (kg)	Dose (mg)
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

ddI in combination with TDF:

- This combination should be avoided, if possible, because of enhanced ddI toxicity.

Pediatric/adolescent dose of ddI when combined with TDF:

- No data on this combination in children or adolescents aged <18 years, but decrease in ddI dose is recommended as in adults.

Adult dose of ddI when combined with TDF:

Body Weight (kg)	Dose (mg)
<60 kg (limited data in adults)	200 mg once daily
≥60 kg	250 mg once daily

- Shake ddI oral solution well before use. Keep refrigerated; solution is stable for 30 days.

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 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 timing doses to avoid giving other medications concurrently with didanosine suspension.
- *Mechanism unknown:* Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir and this combination should be avoided if possible.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* Risk of pancreatitis and peripheral neuropathy is increased with use of some nucleoside reverse transcriptase inhibitors (NRTIs) (such as stavudine). The 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, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Pancreatitis (less common in children than in adults, more common in adults when used in combination with tenofovir or stavudine), increased liver enzymes, and retinal depigmentation and optic neuritis 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:* Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use in adults.[1-3] In adults, use of didanosine may be associated with increased risk of myocardial infarction.[4]

Resistance: The International Antiviral 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 Use: Didanosine is Food and Drug Administration (FDA) approved for use in children as part of a dual-NRTI backbone in combination antiretroviral therapy (cART).

Recommended doses of didanosine oral solution in children have traditionally been 90 to 150 mg/m^2 body surface area per dose twice daily. Doses higher than 180 mg/m^2 body surface area twice daily are associated with increased toxicity.[5] The pharmacokinetic (PK) variable of greatest pharmacodynamic significance is the area under the curve (AUC), with virologic response best when didanosine AUC ≥0.60 mg*h/L.[6, 7] In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg/m^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with adequate exposure predicted in 88% of patients at a dose of 120 mg/m^2 body surface area twice daily,[7] which is the currently recommended dose for children aged 8 months to 3 years.

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m^2 body surface area per dose twice daily, increasing to 120 mg/m^2 body surface area per dose twice daily at age 8 months. However, 2 small studies suggest that a higher AUC is seen in infants aged <6 weeks and that a dose of 100 mg/m^2 body surface area per day (either as 50 mg/m^2 body surface area per dose twice daily or 100 mg/m^2 body surface area once daily) in infants aged <6 weeks achieves AUCs consistent with those for higher doses in older children.[8, 9] Therefore, because these PK differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in that age group, the Panel recommends a dose of 50 mg/m^2 of body surface area twice daily for infants younger than 3 months.

A once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing. In a study of 10 children aged 4 to 10 years, EC didanosine (Videx EC) administered as a single dose of 240 mg/m^2 body surface area once daily was shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine.[8] The resultant intracellular (active) drug concentrations are unknown. In 24 HIV-infected children, didanosine oral solution at a dose of 180 mg/m^2 body surface area once daily was compared with 90 mg/m^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group.[10] Long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution or EC beadlet capsules) was reported in 37 treatment-naive children aged 3 to 21 years.[11] The didanosine dose used in that study was 240 mg/m^2/dose once daily, and PK analysis showed no dose changes were needed to reach PK targets.[11] A European trial of once-daily combination therapy in 36 children aged 3 to 11 years that included didanosine at a dose of 200 to 240 mg/m^2 body surface area demonstrated safety and efficacy with up to 96 weeks of follow up.[12] In 53

children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg/m^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy.[13] In 51 children (median age 6.0 years, range 2.5 to 15.0 years) in Burkina Faso, the once-daily combination of didanosine-lamivudine-efavirenz resulted in week-48 viral load <300 copies/mL in 81% of treated participants. That study used didanosine at a dose of 240 mg/m^2/day, administered in the fasting state as tablets with a separate antacid (not enteric-coated capsules).[6]

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and it may decrease medication adherence by increasing regimen complexity. A comparison showed that regardless of whether didanosine oral solution was given to children with or without food systemic exposure measured by AUC was similar; absorption of didanosine administered with food was slower and elimination more prolonged.[14] To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food.[15, 16] A European study dosed didanosine oral solution as part of a four-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction, and showed good virologic outcome with up to 96 weeks of follow-up.[17]

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Emtricitabine (FTC, Emtriva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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)
- *With TDF and rilpivirine (RPV):* 200 mg FTC + 300 mg TDF + 25 mg RPV (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose (aged 0–<3 months):

- *Oral solution:* 3 mg/kg once daily.

Pediatric dose (aged ≥3 months–17 years):

- *Oral solution:* 6 mg/kg (maximum dose 240 mg) once daily. (Higher maximum dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.)
- *Capsules (for children who weigh >33 kg):* 200 mg once daily.

Adolescent (aged ≥18 years)/adult dose:

- *Oral solution:* 240 mg (24 mL) once daily.
- *Capsules:* 200 mg once daily.

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and ≥40 kg) and adult dose:* 1 tablet once daily.
- See efavirenz section for pregnancy warning.

Complera

- *Adult dose (aged ≥18 years):* 1 tablet once daily.

Selected Adverse Events

- Minimal toxicity.
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus (HBV)-coinfected patients who discontinue FTC.
- Hyperpigmentation/skin discoloration on palms and/or soles.

Special Instructions

- FTC can be given without regard to food; however, administer Atripla on an empty stomach because it also contains EFV.
- FTC oral solution can be kept at room temperature up to 77°F (25°C) if used within 3 months; refrigerate for longer term storage.
- Before using FTC, screen patients for HBV.

Metabolism

- Limited metabolism: No cytochrome P (CYP) 450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- Dosing of FTC in patients with renal impairment: Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with creatinine clearance (CrCl) <50

Stribild: • *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food.	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. • Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease. • If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Do not use emtricitabine in combination with lamivudine because the agents share similar resistance profiles and lack 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.
- *Use with Stribild:* If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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/hepatitis B virus-co-infected patients who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance: The International Antiviral 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 Use: Emtricitabine is Food and Drug Administration (FDA)-approved for once-daily administration in children starting at birth. Owing to its once-a-day dosing, minimal toxicity, and pediatric pharmacokinetic (PK) data, emtricitabine is commonly used as part of a dual-NRTI backbone in antiretroviral therapy (ART).

A single-dose PK study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children ages 2 to 17 years.[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 (ARV) drugs.[2, 3] PK results were similar to the preceding dose-finding study.[1] Follow-up data extending to Week 96 indicated that 89% of the ARV-naive and 76% of the ARV-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (74% of ARV-naive children and 62% of ARV-experienced children at <50 copies/mL). Minimal toxicity was observed in this trial.

In PACTG P1021, emtricitabine 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, was studied in 37 ARV-naive HIV-infected children aged 3 months to 21 years.[2] Eighty-five percent of children achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm^3 at Week 96.

A study in South Africa evaluated the PKs of emtricitabine in 20 HIV-exposed infants aged <3 months, given emtricitabine as 3 mg/kg once daily for two, 4-day courses, separated by an interval of ≥2 weeks.[4] Emtricitabine exposure (area under the curve [AUC]) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients aged >3 months receiving the recommended emtricitabine dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200-mg emtricitabine dose (AUC approximately 10 hr*ug/mL). Over the first 3 months of life, emtricitabine AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (N = 6) receiving a single dose of emtricitabine 3 mg/kg after a single maternal dose of 600 mg during delivery, the AUC exceeded that seen in adults and older children, but the half-life (9.2 hrs) was similar.[5] Extensive safety data are lacking in this age range.

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Lamivudine (3TC/Epivir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 HBVa)

Tablets: 150 mg (scored) and 300 mg (generic and Epivir); 100 mg (Epivir HBV[a])

Combination tablets:

- *With zidovudine (ZDV):* 150 mg 3TC + 300 mg ZDV (generic and 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)

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The strength of 3TC in Epivir HBV solution and tablet was maximized for treatment of hepatitis B virus (HBV) only. If Epivir HBV is 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 is appropriate for use in children who require a 100 mg 3TC dose for treatment of HIV infection.

Dosing Recommendations

Neonate/infant dose (age <4 weeks) for prevention of transmission or treatment:

- 2 mg/kg twice daily.

Pediatric dose (age ≥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 (age ≥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.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic hepatitis B infection.

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

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

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 and weight >50 kg)/adult dose:*
  1 tablet once daily.

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 nucleoside reverse transcriptase inhibitors (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 Antiviral 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 Use: Lamivudine is Food and Drug Administration (FDA)-approved for use in children aged ≥3 months, and it is a common component of most nucleoside backbone regimens.

Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral (ARV) 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.[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] Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150 mg scored tablets.[19, 20]

Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.[11] A population pharmacokinetic (PK) analysis of infants receiving lamivudine affirms that adjusting the dose of lamivudine from 2 mg/kg to 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure.[21] For infants in the first 2 weeks of life, weight-band dosing has also been used. In HPTN 040, all infants weighing >2000 g received 6 mg twice daily and infants weighing ≤2000 g received 4 mg twice daily for 2 weeks. These doses resulted in similar lamivudine exposure as in infants

receiving the standard 2 mg/kg/dose twice daily dosing schedule for neonates.[22]

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of 8 mg/kg leads to area under the curve $(AUC)_{0\text{-}24}$ values similar to 4 mg/kg twice daily but C_{min} values significantly lower and C_{max} values significantly higher in children ages 1 to 18 years.[23] Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children ages 2 to 13 years in the PENTA-13 trial[2] and in children 3 to 36 months of age in the PENTA 15 trial.[24] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. $AUC_{0\text{-}24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children ages 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent $AUC_{0\text{-}24}$ and good clinical outcome (disease stage and CD4 T lymphocyte [CD4 cell] count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years.[25] All three studies enrolled only patients who had low viral load or were clinically stable on twice-daily lamivudine before changing to once-daily dosing. Nacro et al studied a once-daily regimen in ARV-naive children in Burkina-Faso composed of non-enteric-coated didanosine (ddI), lamivudine, and efavirenz. Fifty-one children ranging in age from 30 months to 15 years were enrolled in this open-label, Phase II study lasting 12 months.[26] The patients had advanced HIV infection with a mean CD4 percentage of 9 and a median plasma RNA of 5.51 $\log_{10}$/copies/mL. At 12-month follow-up, 50% of patients had a plasma RNA <50 copies/mL and 80% were <300 copies/mL with marked improvements in CD4 percentage. Twenty-two percent of patients harbored multi-class-resistant viral strains. While PK values were similar to the PENTA and ARROW trials, the study was complicated by use of non-enteric-coated ddI, severe immunosuppression, and non-clade B virus. In addition, rates of virologic failure and resistance profiles were not separated by age. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged 3 years and older with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 cell count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of lamivudine can be used effectively to initiate antiretroviral therapy in children.

Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine

Study/(reference)	PENTA 15[24]		PENTA 13[2]		ARROW[25]	
	Europe		Europe		Uganda	
N	17		14		35	
	2		5		7	
Sex (% male)	56%		43%		42%	
	78%		Not Reported		100%	
	11		19		19	
Concurrent PI use	8		1		0	
Dosing interval (hours)	12	24	12	24	12	24
Administered dose (mg/kg)	4.04	8.02	4.05	8.1	4.7	9.6
$AUC_{0\text{-}24}$ (mg*hr/L)	9.48[a]	8.66[a]	8.88[a]	9.80[a]	11.97[a]	12.99[a]
C_{max} (mg/L)	1.05[a]	1.87[a]	1.11[a]	2.09[a]	1.80[a]	3.17[a]
C_{min} (mg/L)	0.08[a]	0.05[a]	0.067[a]	0.056[a]	0.08[a]	0.05[a]
Cl/F/kg (L/hr/kg)	0.79[a]	0.86[a]	0.90[a]	0.80[a]	0.79[a]	0.72[a]

Data are medians except as noted.

[a] Geometric mean

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 unphosphorylated lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once- and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents aged 16 and older who weigh 50 kg or more.[27, 28]

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Stavudine (d4T, Zerit) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, 40 mg

Generic: d4T capsules and solution have been approved by the Food and Drug Administration (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 (at least 14 days old and weighing <30 kg):

- 1 mg/kg twice daily

Adolescent (≥30 kg)/adult dose:

- 30 mg twice daily.

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors [NRTIs]). The risk is increased when used in combination with ddI.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- d4T can be given without regard to food.
- Shake d4T oral solution well before use. Keep refrigerated; the solution 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 because of virologic antagonism.

- *Overlapping toxicities:* The 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.
- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in HIV/hepatitis C virus co-infected patients receiving combination antiretroviral therapy (ART), interferon, and ribavirin.

Major Toxicities:

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral sensory neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a history of peripheral neuropathy, and in those patients receiving other drugs associated with neuropathy. 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, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant women. This combination should not be used for initial therapy. Risk factors found to be associated with lactic acidosis in adults include female gender, obesity, and prolonged nucleoside exposure.[1]
- *Rare:* Increased liver enzymes and hepatic toxicity which may be severe or fatal. Neurologic symptoms including rapidly progressive ascending neuromuscular weakness are most often seen in the setting of lactic acidosis.

Resistance: The International Antiviral 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 Use: Although stavudine is FDA-approved for use in children, its use is limited because it carries a higher risk of side effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Data from multiple pediatric studies of stavudine alone or in combination with other antiretroviral agents demonstrate that stavudine appears safe and is associated with clinical and virologic response.[2-8] In resource-limited countries, stavudine is frequently a component of initial ART therapy with lamivudine and nevirapine in children, 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 T lymphocyte count and complete viral suppression in 50% to 80% of treatment-naive children.[9-12] In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving cotrimoxazole prophylaxis.[13]

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.[14, 15] 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 more often with stavudine use.[15] Peripheral neuropathy is an important

toxicity associated with stavudine but appears to be less common in children than in adults.[3, 16] In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children.[15] Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.[17-20] Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy, with 9 children demonstrating lipoatrophy.[21] Among 90 children receiving stavudine, lamivudine, and either nevirapine or efavirenz, 65% developed lipodystrophy by 33 months.[22] Among 100 pre-pubertal African children, the prevalence of lipoatrophy was found to be 37% with a strong correlation with duration on stavudine therapy.[23] Improvements in lipodystrophy were observed among Thai children after substitution of stavudine with zidovudine.[24]

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine (ddI).[25-27] In adults, female gender, higher body mass index (BMI), and lower initial CD4 cell count are risk factors for developing lactic acidosis and hyperlactatemia.[1] 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.[28] (For additional information on lactic acidosis see Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.)

Many of the above-mentioned adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues.[25, 29-31] In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.[32]

The World Health Organization recommends that stavudine be phased out of use because of unacceptable toxicity, with a strong recommendation that a maximum stavudine dose of 30 mg twice daily be used instead of the FDA-recommended 40 mg twice daily in patients weighing 60 kg or more.[33, 34] Several studies have compared the efficacy and toxicity of the two doses: HIV suppression was found to be similar in adults treated in South Africa with either the 30-mg or 40-mg dose;[35] in adults treated in South Africa, incidence of peripheral neuropathy was significantly lower in the 30-mg than in the 40-mg group, but the overall incidence was considered to be unacceptably high.[36] Lipoatrophy and peripheral neuropathy are more likely to occur with higher doses but the risk of lactic acidosis is associated with female gender and a high BMI.[33] Efficacy data are limited comparing the 30-mg and 40-mg doses given twice daily, but incidence of lipoatrophy and peripheral neuropathy are reduced when the lower doses are used.

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.[37] These early studies were conducted at a time when treatment options were limited and many children had failure to thrive. The authors in this early PK study state that stavudine distributes in total body water and because total body weight correlates well with lean body mass (or weight) stavudine dosages in obese children should be based on lean body weight.[37]

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, the appropriate dose drawn up into an oral syringe, and administered immediately. Because plasma exposure is equivalent with stavudine administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.[38]

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Oral powder: 40 mg per 1 g of oral powder (1 level scoop = 1 g oral powder; supplied with dosing scoop)

Tablet: 150 mg, 200 mg, 250 mg, and 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)
- *With FTC + rilpivirine (RPV):* 200 mg FTC + 25 mg RPV + 300 mg TDF (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose:
Not FDA approved or recommended for use in neonates/infants aged <2 years.

Pediatric dose (aged ≥2 years to <12 years)*:

- 8 mg/kg/dose once daily.

Oral powder dosing table

Body Weight Kilogram (kg)	Oral Powder Once Daily Scoops of Powder
10–<12	2
12–<14	2.5
14–<17	3
17–<19	3.5
19–<22	4
22–<24	4.5
24–<27	5
27–<29	5.5
29–<32	6
32–<34	6.5
34–<35	7
≥35	7.5

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density (BMD)

Special Instructions

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix oral powder in 2–4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the oral powder with liquid: the powder may float on the top even after vigorous stirring.
- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains EFV, the combination tablet should be administered on an empty stomach.
- Given the potential for TDF-induced changes in renal tubular function, some panel members recommend monitoring for proteinuria and glycosuria every 6–12 months.

Tablets dosing table (aged ≥2 years and weight ≥17 kg)

Body Weight Kilogram (kg)	Tablets Once Daily
17–<22	150 mg
22–<28	200 mg
28–<35	250 mg
≥35	300 mg

Adolescent (aged ≥12 years and weight ≥35 kg)* and adult dose:

- 300 mg once daily

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

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and weight ≥40kg) and adult dose:* 1 tablet once daily.

Complera

- *Adult dose:* 1 tablet once daily in treatment-naive adults. Administer with a meal.

Stribild

- *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food

TDF in combination with didanosine (ddI):

- The combination of TDF and ddI should be avoided if possible. If used, ddI dose requires modification. See section on ddI.

TDF in combination with atazanavir (ATV):

- When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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 (CrCl).
- Atripla and Complera (fixed-dose combinations) 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.
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

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 disoproxil fumarate (tenofovir).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors (PIs):* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir co-administered 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 co-administered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.
- *Use with Stribild:* If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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 (BMD) have been reported in both adults and children taking tenofovir; 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 Antiviral 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 Use: Tenofovir is Food and Drug Administration (FDA) approved for use in children aged ≥2 years when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

The standard adult dose of tenofovir approved by the FDA for adults and children aged ≥12 years and weight ≥35 kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 mg/m^2/dose used in early studies in children.[1]

In adults, the recommended dose is highly effective.[2, 3]

In children aged 12 to <18 years, no difference in viral load response was seen between 2 treatment groups in a randomized, placebo-controlled trial of tenofovir 300 mg once daily or placebo, plus an optimized background regimen, in 87 treatment-experienced adolescents in Brazil and Panama.[4-6] Subgroup analyses suggest this lack of response was from imbalances in viral susceptibility to the optimized background regimens.

In children aged 2 to <12 years, tenofovir 8 mg/kg/ dose once daily showed non-inferiority to zidovudine- or stavurdine-containing cART over 48 weeks of randomized treatment using a snapshot analysis (product label). This was a switch study in children aged 2 to 12 years with viral load <400 copies/mL during treatment with zidovudine or stavudine as part of cART, randomized to continue their zidovudine or stavudine (N=49) or switch to tenofovir (N=48) while continuing other components of the regimen (Gilead study 352).[4]

Other pediatric studies have also shown that virologic success is related to prior treatment experience. In 115 pediatric patients treated with tenofovir, viral load decreased to <50 copies/mL at 12 months in 50% of patients on first-line therapy, 39% of patients on second-line therapy, and 13% of patients on third-line or subsequent therapy.[7] This cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Virologic success is also related to drug exposure. In a study using a median daily dose of 208 mg/m^2, [8] lower single-dose and steady-state area under the curve (AUC) were associated with inferior virologic outcome.

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir 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 maximum plasma concentration (C_{max}) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg.[1, 9] Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure.[1] This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower-than-anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir.[10]

Further studies are needed of tenofovir PK and clinical outcomes in children, especially when used in combinations that do not include lopinavir and/or ritonavir.

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (Tanner Stages 1 and 2) may be at higher risk than children with more advanced development (Tanner Stage ≥3).[1, 11, 12] In a Phase I/II study of an investigational 75-mg formulation of tenofovir in 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48.[1] Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks.[13] 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.[8, 13] In a second study of 6 patients who received the commercially available, 300 mg formulation of tenofovir, 2 pre-pubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her cART regimen with subsequent recovery of BMD.[14] Loss of BMD at 48 weeks was associated with higher drug exposure.[8]

In the industry-sponsored study that led to FDA approval of tenofovir in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm[4, 5] (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf).

In the Gilead switch study (352) in children aged 2 to 12 years over the 48 weeks of randomized treatment, total body BMD gain was less in the tenofovir group than in the zidovudine or stavudine group, but the mean rate of lumbar spine BMD gain was similar between groups. At 48 weeks all participants were offered tenofovir, and for the participants who were treated with the drug for 96 weeks, total body BMD *z* score declined by -0.338 and lumbar spine BMD *z* score declined by -0.012.[4]

Not all studies of tenofovir in children have identified a decline in BMD.[15, 16] No effect of tenofovir on BMD was found in a study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz.[17] All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen.[18]

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in those with higher tenofovir trough plasma concentrations.[19] Possible tenofovir -associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance (CrCl), 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.[20] Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine.[21] Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland.[7] Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir.[22] 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 cART.[23] Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovior-containing antiretroviral regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range.[24] However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years.[25] Of 89 participants who received tenofovir in Gilead study 352 (median drug exposure 104 weeks), 4 discontinued from the study for renal tubular dysfunction, and 3 of whom had hypophosphatemia and decrease in total body or spine BMD *z* score.[4]

Given the potential for BMD loss in children treated with tenofovir, some experts recommend obtaining a DXA before 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). 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 early adolescence is concerning and favors judicious use of tenofovir in this age group.

The taste-masked granules that make up the oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed in the vehicle, if allowed to sit too long, the taste becomes bitter.

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Zidovudine (ZDV, AZT, Retrovir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 or intravenous (IV) infusion: 10 mg/mL

Generic: ZDV capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Combination tablets:

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

Dosing Recommendations

ZDV dose for neonates/infants (<6 weeks of age) for prevention of transmission or treatment (Note: standard neonate dose may be excessive in premature infants)**:**

Gestational Age (weeks)	ZDV Oral Dosing	ZDV Intravenous Dosing (if unable to tolerate oral agents)
≥35 weeks	4 mg/kg of body weight every 12 hours	3 mg/kg of body weight IV every 12 hours
≥30–<35 weeks	2 mg/kg of body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg of body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg of body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg of body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy.

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develop in patients receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells and platelets.

Pediatric dose (6 weeks to <18 years of age):

- *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 (age ≥18 years)/adult dose:

- 300 mg twice daily.

Combivir

Adolescent (weight ≥30 kg)/adult dose:

- 1 tablet twice daily.

Trizivir

Adolescent (weight ≥40 kg)/adult dose:

- 1 tablet twice daily.

Metabolism

- Metabolized to AZT glucuronide, which is renally excreted.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal insufficiency.
- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance (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 nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine should not be administered in combination with stavudine because of virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Incidence of neutropenia may be increased in infants receiving lamivudine.[1]
- *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.[2]

Resistance: The International Antiviral 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).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy.[3]

Pediatric Use: Zidovudine is frequently included as a component of the NRTI backbone for antiretroviral therapy.[4-20] Pediatric experience with zidovudine both for treatment of HIV and for prevention of mother-to-child transmission (PMTCT) is extensive.

Perinatal trial PACTG 076 established that zidovudine prophylaxis given during pregnancy, labor, and delivery, and to the newborn reduced risk of perinatal transmission of HIV by nearly 70%[21] (see the 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 for further discussion on the use of zidovudine for PMTCT of HIV). Although the PACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice daily oral infant dosing for prophylaxis. Zidovudine 4 mg/kg of body weight every 12 hours is now recommended for neonates/infants >35 weeks of gestation for prevention of transmission or treatment (see *Perinatal Guidelines*).

Overall, zidovudine pharmacokinetics (PKs) in pediatric patients aged >3 months are similar to those in adults. 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.[22] PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age.[5] 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.[23]

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Appendix A: Pediatric Antiretroviral Drug Information

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

Efavirenz (EFV, Sustiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Combination Tablets:

- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  FTC 200 mg + TDF 300 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

- EFV is not approved for use in neonates/infants.

Pediatric dose:

- *Children aged <3 years:*
  No data are currently available on the appropriate EFV dosage for children aged <3 years.
- *Children aged ≥3 years and body weight ≥10 kg:*
  Administer EFV once daily:

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

* The dose in mg can be dispensed in any combination of capsule strengths.

† Some experts recommend a dose of 367 mg/m^2 of body surface area (maximum dose 600 mg) because of concern for underdosing, especially at the upper end of each weight band (see *Pediatric Use* for details).

Adolescent (body weight ≥40 kg)/adult dose:

- 600 mg once daily.

Selected Adverse Events

- Rash
- Central nervous system (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Potentially teratogenic
- Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors.

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. Avoid administration with a high-fat meal because of potential for increased absorption.
- Administer Atripla on an empty stomach.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- EFV should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).

Atripla

- Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.
- *Adult dose:* One tablet once daily
- CYP3A4 and CYP2B6 substrate.
- 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 (CrCl) of <50 mL/minute or in patients on dialysis.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers having higher risk of toxicity. (See text for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

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

- *Metabolism:* Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions. Importantly, dosage adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities, such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.
- *Rare:* Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as Food and Drug Administration (FDA) Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of

avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health).

Resistance: The International Antiviral 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 Use: Efavirenz is FDA-approved for use as part of antiretroviral therapy in children aged 3 years or older who weigh at least 10 kg. Limited pharmacokinetic (PK) data in children younger than age 3 or who weigh less than 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 an investigational liquid formulation.[1] Thus, efavirenz is not recommended for use in children younger than age 3 years 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. P1070 is an ongoing study collecting data on efavirenz dosing in HIV-infected and HIV/tuberculosis-co-infected children younger than age 3 years. In addition, efavirenz should be used with caution in adolescent women of childbearing age because of the potential risk of teratogenicity.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 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.[2, 3] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults.[4, 5]

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1 mcg/mL in adults.[6] 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 levels less than or equal to 400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL).[7] In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration (C_{min}) levels greater than 1.1 mcg/mL or area under the curve (AUC) greater than 51 mcg*h/mL.[8] Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal.[2, 8-11] Therefore, some experts recommend therapeutic drug monitoring with efavirenz and possibly use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered efavirenz dose was 13 mg/kg (367 mg/m^2) and the range was from 3 to 23 mg/kg (69–559 mg/m^2).[7] A PK study in 20 children aged 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 PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.[12] Therapeutic drug monitoring can be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported 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 during the first 2 weeks of treatment.[13] Although severe rash and Stevens-Johnson syndrome (SJS) have been reported, they are rare. In adults, CNS symptoms have been reported in more than 50% of patients.[14] These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. Ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric adverse effects. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations.[6, 15-18] 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[13] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.[3] CNS adverse effects may be harder to detect in children because of the difficulty in assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

Therapeutic drug monitoring (TDM) can be considered for children with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In that situation, it is reasonable for a clinician to use therapeutic drug monitoring to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.[19, 20] 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.

Efavirenz should not be used by women who desire to become pregnant or who do not use effective, consistent contraception. Efavirenz should not be used throughout the first trimester of pregnancy because of the potential risk of teratogenicity[21] (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*[22]). Alternative ARV regimens that do not include efavirenz should be strongly considered for use in sexually active adolescent females because of the potential for inconsistent use of contraception and the high risk of unintended pregnancy.

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Etravirine (ETR, Intelence, TMC 125) (Last updated November 15, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets: 25 mg, 100 mg, and 200 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

Antiretroviral-experienced children and adolescents aged 6-18 years (and weighing at least 16 kg):

Weight in kilograms (kg)	Dose
16 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
≥30 kg	200 mg twice daily

Adult dose (antiretroviral-experienced patients):

- 200 mg 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) of ETR is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to ETR.
- ETR tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medication, stir well until the water looks milky; if desired, add more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm [>40°C] drinks, or carbonated beverages should be avoided). Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure 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: Dose adjustment is not required in

patients with renal impairment.

Metabolism

- ETR is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (Pgp). It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple drug interactions (see below).

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

- Etravirine is associated with multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions with ETR.
- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors. It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, efavirenz, or rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,[1] but no dose adjustment is currently recommended when etravirine and raltegravir are used together.

Major Toxicities:

- *More common:* Nausea, diarrhea, and 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 (more severe):* Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (HSRs) (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 HSRs 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 Use: Etravirine is FDA-approved for use in antiretroviral-experienced children and adolescents aged 6 to 18 years.

A Phase I dose-finding study involving children aged 6–17 years, with virologic suppression on a stable lopinavir/ritonavir-containing regimen compared doses of 4 mg/kg twice daily and 5.2 mg/kg twice daily using both the investigational 25-mg tablets and the available 100-mg formulation.[2] Etravirine therapy was added for 8 days and pharmacokinetic (PK) sampling and analysis were performed. Among 17 children given 4 mg/kg twice daily, the PK parameters AUC_{12h} and C_{min} were below preset statistical targets compared with these parameters in adults. By comparison, acceptable PK were observed for participants who received 5.2 mg/kg twice daily, including 12 patients aged 6 to <12 years, and 9 study participants ages 12 to 17 years. The higher dose (5.2 mg/kg twice daily; [maximum 200 mg per dose]) was chosen for evaluation in the PIANO study (TMC125-C213), a single-arm, Phase II trial evaluating the PK, safety, tolerability, and efficacy of etravirine in 101 ARV treatment-experienced HIV-1 infected pediatric subjects aged 6 to <18 years and weighing ≥16 kg.[3] Subjects eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA of at least 500 copies/mL and viral susceptibility to etravirine at screening. The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/mL, and the median baseline CD4 T lymphocyte (CD4 cell) count was 385 x 10^6 cells per mm^3. At Week 24, 67% of these pediatric subjects had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. The mean CD4 cell count increase from baseline was 112 x 10^6 cells per mm^3. The population PK data from this Phase II trial (101 treatment-experienced children aged 6–17 years) revealed slightly lower etravirine exposures in adolescents (aged 12–17 years) compared with children aged 6 to 11 years and with adults (see table below).

	Mean AUC_{12} (ng*h/mL)	**Mean C_{0h} (ng/mL)**
Children aged 6–11 years (N=41)	5764	381
Adolescents aged 12–17 years (N=60)	4834	323
All Pediatric Participants	5236	347
Adults	5506	393
AUC_{12} = Area under the curve for 12h post dose; C_{0h} = pre-dose concentration during chronic administration.		

The frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adult subjects, except for rash, which was observed more frequently in pediatric subjects. The most common adverse drug reactions (in at least 2% of pediatric subjects) were rash and diarrhea. Rash (≥Grade 2) occurred in 15% of pediatric subjects. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared with male subjects.

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluted in a multicenter retrospective study of 23 multidrug-resistant pediatric patients with a median age of 14.2 years (interquartile range 12.5 to 15.8 years).[4] The median baseline HIV-1 RNA was 4.5 $\log_{10}$ HIV-1 RNA copies/mL and the median CD4 T-cell count was 445 cells/mm^3. The backbone regimen included at least two fully active drugs in 91% of patients. During a median of 48.4 weeks of follow-up, 20 patients (87%) achieved HIV-1 RNA<400 copies/mL and 18 of 23 (78%) achieved HIV-1 RNA<50 copies/mL. No patients showed complete resistance to etravirine after follow up but 3 of the 21 patients who interrupted etravirine treatment because of virological or immunological failure had single resistance mutations at baseline.

The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multi-center retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit et al found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4.[5]

Etravirine is often combined with ritonavir-boosted darunavir for treatment of HIV-infected adults with prior virologic failure. King et al[6] examined PK data from 37 pediatric patients receiving this combination, all receiving the maximum 200 mg etravirine dose. For both drugs, the estimated 90% confidence intervals for AUC and C_{min} fell below targeted lower limits defined using data from studies in adults. While this combination has been effective in a small cohort of HIV-infected adolescents,[7] these data suggest a need for continued study of PK interactions involving etravirine and other ARV agents in pediatric patients.

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Nevirapine (NVP, Viramune) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets: 200 mg, extended-release 400 mg

Suspension: 10 mg/mL

Dosing Recommendations

Neonate/infant dose (aged <14 days):

- When used for prevention of mother-to-child transmission of HIV see *Perinatal Guidelines*. Treatment dose not defined for infants aged ≤14 days.

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

Aged <8 years:

- 200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

Aged ≥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 age 8 years; rather, the mg dose is left static to achieve the appropriate mg/m^2 dosage as the child grows, as long as there are no untoward effects.

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P45-metabolizing enzymes, which results in increased drug clearance. 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

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.
- 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*).
- NVP XR tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see text below).
- 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 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.

Note: 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.

- 400 mg XR once daily (not approved for use in children)

Note: Initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg administered once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release NVP, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow NVP extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of NVP at the same time.

- *NVP in combination with lopinavir/ritonavir (LPV/r):*

A higher dose of LPV/r may be needed. See LPV/r section.

- 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.

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; auto-induction of metabolism occurs in 2 to 4 weeks, with a 1.5- to 2-fold increase in clearance. Potential exists for multiple drug interactions. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than efavirenz. Altered adverse effect profiles related to elevated nevirapine levels have not been documented, probably because there are alternative CYP metabolic pathways for nevirapine.[1] Please see efavirenz section for further details.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be co-administered 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 (i.e., fever, oral lesions, conjunctivitis, or blistering), 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 a patient's overall ability to tolerate the regimen and the current antiviral response.

- *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). Most cases occur in the first 12 weeks of therapy and 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 T lymphocyte (CD4 cell) count at time of therapy initiation (CD4 cell count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). In children, recent results indicate that there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.[2] 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 Use: Nevirapine is U.S. Food and Drug Administration (FDA) approved for use in children from infancy onwards and remains a mainstay of therapy, especially in resource-limited settings. It has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI).[3-11]

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission, nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-based ART to control virus load. 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 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, $P = 0.027$.[12] A comparison study of nevirapine versus lopinavir/ritonavir in children aged 6 to 36 months not previously exposed to nevirapine has reported similar results, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[13]

Body surface area has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid under dosing of nevirapine because a single point mutation in the HIV genome may confer non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children (aged ≤8 years) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.[8, 9] Because of this, it is recommended that dosing for children aged <8 years be 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children aged 8 years, 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 dosage 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 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

The potential for under dosing with an increased risk of resistance has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of nevirapine is initiated with a single daily dose during the first 2 weeks of treatment to allow for auto-induction of the liver enzymes CYP3A and CYP2B6 (which are involved in nevirapine metabolism). Studies, largely in adult cohorts, indicated the potential for greater drug toxicity without this half-dose lead-in.[14] The CHAPAS-1 Trial[15] randomized 211 children to initiate ART with either half dose or full-dose nevirapine. Children were followed for a median of 92 weeks (68–116 weeks), and there was no difference in grade 3 or 4 adverse events between the 2 groups. The full-dose nevirapine group had a statistically significant increase in grade 2 rash, but most subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. Additional trials are either in development or are under way to further evaluate the potential of initiating nevirapine therapy at full dose in treatment-naive children. Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,[16] and the results of CHAPAS-1, the Panel recommends restarting nevirapine at full dose in children who interrupt therapy for 14 days or less.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients on the basis of 2 trials: VERxVE and TRANxITION. VERxVE[17] enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. VERxVE and TRANxITION have shown equivalent efficacy, adverse effect, and CD4 profiles through 48 and 24 weeks, respectively.[18] Trials are under way on use of extended-release nevirapine in patients aged <18 years.

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Rilpivirine (RPV, Edurant, TMC 278) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Tablet: 25 mg

Combination Tablet:
- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  RPV 25 mg + FTC 200 mg + TDF 300 mg (Complera)

Dosing Recommendations

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

Pediatric dose:
- Not approved for use in children. A clinical trial in treatment-naive adolescents (aged 12–18 years) is under way.

Adolescent (>18 years of age)/adult dose (antiretroviral [ARV]-naive patients only):
- 25 mg once daily

Selected Adverse Events

- Depression, mood changes
- Insomnia
- Headache
- Rash

Special Instructions

- Instruct patients to take rilpivirine with a meal of at least 500 calories (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Use rilpivirine with caution when co-administered with a drug with a known risk of torsade de pointes (http://www.qtdrugs.org/).
- Use rilpivirine with caution in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.

Drug Interactions:

- *Metabolism:* Rilpivirine is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before rilpivirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Insomnia, headache, and rash.
- *Less common (more severe):* Depression or mood changes.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html).

Pediatric Use: The pharmacokinetics, safety, and efficacy of rilpivirine in pediatric patients have not been established. An international trial currently under way is investigating a 25-mg dose of rilpivirine in combination with two nucleoside reverse transcriptase inhibitors in antiretroviral-naive children aged 12 to 18 years who weigh at least 40 kg.

Appendix A: Pediatric Antiretroviral Drug Information

Protease Inhibitors

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Fosamprenavir (FPV, Lexiva)

Indinavir (IDV, Crixivan)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Nelfinavir (NFV, Viracept)

Ritonavir (RTV, Norvir)

Saquinavir (SQV, Invirase)

Tipranavir (TPV, Aptivus)

Atazanavir (ATV, Reyataz) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

- Data are insufficient to recommend dosing in children aged <6 years.

For children aged ≥6 to <18 years:

Weight (kg)	Once-Daily Dose
15–<20 kg	ATV 150 mg + RTV 100 mg, both once daily with food
20–<32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32–<40 kg	ATV 250 mg* + RTV 100 mg, both once daily with food
≥40 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Dose in mg requires two different capsule strengths of ATV. Additional patient education should be considered to avoid dosing errors (see text for discussion).

- *For treatment-naive pediatric patients who do not tolerate ritonavir (RTV):* **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.** Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see *Pediatric Use*).
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Additional patient education should be considered to avoid dosing errors when prescribing ATV 250 mg because this dose requires 2 different capsule strengths of ATV.
- Because ATV can prolong the electrocardiogram (ECG) PR interval, use ATV 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; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing ATV when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.

Adolescent (aged ≥18–21 years)/adult dose:
Antiretroviral-naive patients:

- ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food (if unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see *Pediatric Use*]).

Antiretroviral-experienced patients:

- ATV 300 mg + RTV 100 mg, both once daily with food.

ATV in combination with efavirenz (EFV) (adults) in therapy-naive patients only:

- ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily 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) (adults):

- 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.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients receiving PPIs should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted ATV. Co-administration of ATV with PPIs is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucoronosyltransferase (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 dosage adjustment 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.

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 cytochrome P (CYP) 3A4 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 with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- A patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug is administered.

- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be co-administered with atazanavir in treatment-experienced patients but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naive adults.
- *Integrase Inhibitors:* Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.
- *Absorption:* Atazanavir absorption is dependent on low gastric pH. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors (PPIs) in adults are as follows:

- *Antacids:* Atazanavir concentrations are decreased when the drug is co-administered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted atazanavir in treatment-naive patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the antiretroviral (ARV) agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2 receptor antagonist (a single dose of an H2 receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-Receptor Antagonists (boosted atazanavir in treatment-naive or -experienced patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H2 receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily for treatment-naive patients or a ≤20-mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (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):* Treatment-experienced patients using both tenofovir and H2-receptor antagonists should be given an increased dose of atazanavir (ATV 400 mg + RTV 100 mg + TDF 300 mg).
- *PPIs:* Coadministration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naive patients are ≤20-mg dose equivalent of omeprazole taken approximately 12 hours before boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with PPIs 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 atrioventricular (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 protease inhibitors (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 hepatitis C are at increased risk).

Resistance: The International Antiviral 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 Use: Atazanavir is FDA-approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children aged ≥6 years.

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 (PK) targets, but only when used at higher doses of atazanavir (on a mg/kg body weight or mg/m^2 body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children older than 6 and younger than 13 years of age required atazanavir dosing of 520 mg/m^2 of body surface area per day of atazanavir capsule formulation to achieve PK targets. Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents aged >13 years required atazanavir dosing of 620 mg/m^2 of body surface area per day.[1] In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir groups but the maximum plasma concentration (C_{max}) was higher and minimum plasma concentration (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 (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.[2] Higher target trough concentrations may be required in protease inhibitor (PI)-experienced patients.

Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[1]

Age range (years)	Was ATV given with RTV boosting?	ATV median dose (mg/m^2*)	ATV median dose (mg*)
6–13 years	No	509	475
6–13 years	Yes	208	200
>13 years	No	620	900
>13 years	Yes	195	350

* Dose satisfied protocol-defined AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM was used to determine patient-specific dosing in this trial.

Regarding toxicity, 8.5% (11 of 129) of patients enrolled in the trial had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (ECG) abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 patients. 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.[3, 4]

A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following atazanavir/ritonavir doses: 150/100 mg (15–<20 kg), 200/100 mg (20–<40 kg), 300/100 mg (≥40 kg)[5] and the current FDA-approved product label recommends these weight-based doses. The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[5] The authors acknowledge that atazanavir/ritonavir at 250/100 mg appeared to be a more appropriate dose than atazanavir/ritonavir at 200/100 mg for the 35 to <40 kg weight group; however, this dose was not recommended in the product label because the 250 atazanavir dosage strength requires the use of 2 different capsule strengths and is prone to dosing errors.[5]

The doses of atazanavir/ritonavir recommended by the Pediatric ARV Guideline Panel are 200/100 mg for pediatric patients weighing 20 to <32 kg and 250/100 mg for patients weighing 32 to <40 kg while the FDA-approved dose of atazanavir/ritonavir is 200/100 mg for pediatric patients weighing 20 to <40 kg. The higher dose of 250/100 mg is recommended by the Pediatric ARV Guideline Panel at the 32 to <40 kg weight band to avoid underdosing. Additional patient education to prevent dosing errors is recommended when 250 mg of atazanavir is prescribed because this dosage requires the use of 2 different capsule strengths of atazanavir.

A population PK study of 51 children with mean age 14.3 years and weight 51 kg that targeted mean adult exposure for a 300/100 mg atazanavir/ritonavir dosage showed that the following atazanavir/ritonavir doses might be an appropriate alternative to the FDA recommendations: 200/100 (25–39 kg), 250/100 mg (39–50 kg) and 300/100 (>50 kg).[6] In addition, simulations suggested that the following doses should be used in children when combined with 300 mg tenofovir disoproxil fumarate (TDF): 250/100 mg for children weighing 35 to 39 kg, then 300/100 mg for children weighing over 39 kg.[6] The authors conclude that these recommendations should be prospectively confirmed.[6]

In a small, single-site study, 23 pediatric patients (median age 16 years) on combination antiretroviral therapy were switched to a once-daily ritonavir-boosted atazanavir-containing regimen because of virologic failure (12 patients) or for treatment simplification (11 patients).[7] Twenty of the patients had previously received PI-based regimens with the median number of two atazanavir-associated mutations acquired before switching to atazanavir/ritonavir. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine. Both tenofovir and buffered didanosine have known drug interactions with atazanavir and can lower plasma concentrations. In this study, atazanavir plasma concentrations were measured at 12 to 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 who previously had undetectable viral loads experienced virologic failure; 6 of 12 patients who previously had virologic failure achieved undetectable viral loads.

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Darunavir (DRV, Prezista) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Oral suspension: 100 mg/mL

Dosing Recommendations

- DRV should not be used without ritonavir (RTV).

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- *Age <3 years:*

Do not use DRV in children younger than age 3 years because of concerns related to seizures and death in infant rats associated with immaturity of the blood-brain barrier and liver metabolic pathways.

- *3 to <18 years of age and weighing ≥10 kg:*

Weight	Dose (both twice daily[a] with food)
10–<11 kg	DRV 200 mg (2 mL) + RTV 32 mg (0.4 ml[b])
11–<12 kg	DRV 220 mg (2.2 mL) + RTV 32 mg (0.4 ml[b])
12–<13 kg	DRV 240 mg (2.4 mL) + RTV 40 mg (0.5 ml[b])
13–<14 kg	DRV 260 mg (2.6 mL) + RTV 40 mg (0.5 ml[b])
14–<15 kg	DRV 280 mg (2.8 mL) + RTV 48 mg (0.6 ml[b])
15–<30 kg	DRV 375 mg (tablets or 3.75 mL oral suspension) + RTV 50 mg (0.6 ml[b])[c]
30–<40 kg	DRV 450 mg + RTV 60 mg (0.8 ml[b])[c]
≥40 kg	DRV 600 mg + RTV 100 mg

[a] *Do not use once-daily dosing in children aged <12 years or in any patient aged <18 years who is treatment-experienced (prior treatment failure). Once-daily dosing*

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- DRV must be administered with food, which increases area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- DRV contains a sulfonamide 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. Careful instruction to caregivers is important. Pill burden may have a negative effect on adherence.
- Store DRV tablets and oral suspension at room temperature (25ºC or 77ºF). Oral suspension should be stored in the original container and shaken well before dosing.
- **Do not use once daily for:** children aged <12 years; for youth ages 12–18 years if treatment experienced (prior treatment failure); or in

(DRV 800 mg + RTV 100 mg can be used in treatment-naive pediatric patients aged 12–18 years and weighing ≥40 kg but is not FDA-approved for this population (see text). Note that the dose in children weighing 10–15 kg is 20 mg/kg body weight per dose, higher than the weight-adjusted dose in heavier (older) children.

[b] *RTV supplied as 80mg/mL oral solution.*

[c] *To enhance palatability—RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation for children ≥20 kg, even though the RTV dose is higher.*

Adolescent (aged ≥18 years)/adult dose (treatment-naive or antiretroviral-experienced with no DRV resistance associated mutations):

- DRV 800 mg + RTV 100 mg, both once daily with food.

Adolescent (aged ≥18 years)/adult dose (treatment experienced with at least one DRV resistance-associated mutation):

- DRV 600 mg + RTV 100 mg, both twice daily with food.

those aged ≥18 years if any of these DRV resistance associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V

Metabolism

- Cytochrome P450 3A4 (CYP3A4) 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 (creatinine clearance [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 P (CYP) 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions.
- Before administration, a 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. Fever and elevated hepatic transaminases. Lipid abnormalities.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (such as hepatitis B or hepatitis C virus co-infection, or those with 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 Use: Darunavir boosted with ritonavir is Food and Drug Administration (FDA) approved for use twice daily in combination with ritonavir in children aged 3 years and older as part of combination antiretroviral therapy (cART), but is not FDA-approved for once-daily use in those younger than age 18 years.

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric participants ages 6 to <18 years and weighing ≥20 kg. The participants had a median age of 14 years (range 6–<18 years) and 71% were male, 54% were white, 30% black, 9% Hispanic, and 8% other race/ethnicity. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least two non-protease inhibitor antiretroviral (ARV) drugs.[1] The study was a two-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 to 15 mg/kg and ritonavir 1.5 to 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 24-hour area under the curve (AUC_{24h}) of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult pharmacokinetic parameters. A pediatric dose 20% to 33% higher than the directly 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 to 19 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily. This resulted in darunavir AUC_{24h} of 123,276ng*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 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 chosen as follows: 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. As reported in the FDA clinical review (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129560.pdf), for the 80 participants the Week 24 viral load was <400 copies/mL and <50 copies/mL in 66% and 51% respectively[2] (FDA snapshot analysis), and only 1 participant withdrew for an adverse event.

In this study, 27 of the 80 participants[1] switched from the ritonavir liquid solution to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. A separate study in 19 Thai children[3] used ritonavir 100 mg twice daily as the boosting ritonavir dose, with darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30 to 40 kg), and 600 mg twice daily (body weight ≥40 kg). The darunavir exposures of twice-daily darunavir doses boosted with 100 mg ritonavir twice daily showed values similar to those obtained with lower ritonavir doses. This regimen was well tolerated and adds further support to boosting with the easier to tolerate 100-mg capsule of ritonavir twice daily even in children as young as aged 6 years or weighing as little as 20 kg. Data are not available to evaluate the safety and tolerability of using ritonavir 100 mg in children who weigh less than 20 kg.

Darunavir oral suspension administered twice daily with ritonavir boosting has been studied in children aged 3 to <6 years and weighing 10 to <20 kg, reported in,[4] and in an FDA Clinical review.[2, 5] This trial was in N = 27 children ages 3 to <6 years who were failing their current antiretroviral therapy regimens and had fewer than 3 darunavir resistance-associated mutations on genotype testing. Participants were enrolled from Argentina, Brazil, India, Kenya, and South Africa. The initial dose for study was darunavir 20 mg/kg with ritonavir 3 mg/kg, both given twice daily, but higher-than-anticipated doses were required to achieve target drug exposures. Therefore, the dose used in these studies in this age and weight group

was increased to darunavir 25 mg/kg body weight combined with ritonavir 3 mg/kg body weight for children between 10 and 15 kg, and darunavir 375 mg plus ritonavir 50 mg for children 15 to <20 kg body weight. After dose adjustment, the darunavir AUC (0–12h), measured as a percent of the adult value, was 128% overall, 140% in the 10 to <15 kg weight band, and 122% in participants who weighed 15 to <20 kg (page 44 in http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf). At study week 24, 16 of 27 (59%) of these treatment-experienced subjects aged 3 to 6 years had viral load <50 copies/mL. This compares to a 75% virologic success rate in the 6- to 12-year-olds, and 39% in subjects aged 12 to 18 years (virologic success defined as viral load <50 copies/mL at 24 weeks) (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287673.pdf). Diarrhea, vomiting, and rash were the most common side effects. The taste of the darunavir liquid is said to be better than the poor taste of the ritonavir needed for PK boosting, which is seen as a greater challenge to palatability.

When the study was completed, re-analysis of the PK data suggested that a dose of darunavir 20 mg/kg plus RTV 3 mg/kg body weight would be acceptable (table), and that re-analysis led to the final dosing recommendations found in the FDA product label.

Table. Darunavir Pharmacokinetic Results from Multiple Studies

Population	N	Dose of DRV/RTV and frequency	AUC_{24h}[a] (mcg*h/mL) median[b]	C_{0h} (ng/mL) median[b]
10–<15 kg[c]	13	20/3 mg/kg twice daily	122.0	3,533
10–<15 kg[c]	4	25/3 mg/kg twice daily	238.0	8,522
15–<20 kg[c]	11	20/3 mg/kg twice daily	108.4	3,387
15–<20 kg[c]	14	25/3 mg/kg twice daily	137.2	4,365
Aged 6–<12 years[d]	24	Weight bands,[d] twice daily	112.8	3,354
Aged 12–<18 years[d]	50	Weight bands,[d] twice daily	132.8	4,059
Adults aged >18 years (3 studies)[e]	285, 278, 119	600/100 mg twice daily	109.4–123.3	3,197–3,539
Once Daily				
Ages 12–17 (mean 14.6)[8]	12	800/100 once daily	87.9	2,196
Adults aged >18 years (2 studies)[e]	335, 280	800/100 once daily	87.8-87.9	1,896- 2,041

[a] For twice-daily (BID) dosing, AUC_{24h} is calculated as 2 times the AUC_{12h}.

[b] When more than two studies are included, a range of medians is listed.

[c] FDA pharmacokinetics review 2011 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf)

[d] Weight band dosing was with darunavir/ritonavir at doses of 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. Data from FDA pharmacokinetics review 2008 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=darunavir&utm_content=10)

[e] Product label

When darunavir plus ritonavir twice daily was used in combination with etravirine in 40 HIV-infected patients aged 11 to 20 years, both darunavir and etravirine exposure were lower than that found in adults.[6] When darunavir plus ritonavir twice daily was used in combination with tenofovir in 13 HIV-infected patients aged 13 to 16 years, both tenofovir and darunavir exposures were lower than those found in adults treated with the same combination.[7]

Although darunavir is approved for once-daily dosing in ARV-naive adults, it should not be used once daily in children less than age 12 years because of more rapid clearance and absence of pediatric data. One small study (N = 12) of once-daily dosing (DRV 800 mg + RTV 100 mg) in treatment-naive adolescents aged 12 to 17 years and weighing ≥40 kg demonstrated good Week 24 virologic responses and darunavir exposures similar to those seen in adults treated with once-daily darunavir (see table above).[8]

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Fosamprenavir (FPV, Lexiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets: 700 mg

Oral suspension: 50 mg/mL

Dosing Recommendations

Pediatric dose (aged >6 months–18 years):

- Unboosted FPV (without ritonavir [RTV]) is FDA-approved for antiretroviral (ARV)-naive children aged 2–5 years, but not recommended by the Panel because of low exposures (see text below).
- Boosted FPV (with RTV) is FDA-approved for ARV-naive infants at least 4 weeks of age and for treatment experienced infants at least 6 months of age; however, the Panel does not recommend use in infants younger than 6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks gestation or greater.

Aged ≥6 months–18 years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension With Ritonavir

Weight	Dose FPV + RTV Both twice daily* with food
<11 kg	FPV 45 mg/kg + RTV 7 mg/kg
11 kg–<15 kg	FPV 30 mg/kg + RTV 3 mg/kg
15 kg–<20 kg	FPV 23 mg/kg + RTV 3 mg/kg
≥20 kg	FPV 18 mg/kg + RTV 3 mg/kg

*Not to exceed the adult dose of FPV 700 mg + RTV 100 mg twice daily.

Note: When administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (FPV has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- FPV tablets with RTV should be taken with food. FPV tablets without RTV can be taken with or without food. Pediatric patients should 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 moiety. 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 before 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.

twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Once-daily dosing is not recommended for any pediatric patient.

Adolescent (aged >18 years)/adult dose:

- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

ARV-naive patients:

- *Boosted with RTV, twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily.
- *Boosted with RTV, once-daily regimen:* FPV 1400 mg + RTV 100–200 mg, both once daily.

Protease inhibitor (PI)-experienced patients:

- FPV 700 mg + RTV 100 mg, both twice daily.

Once-daily administration of FPV + RTV is not recommended.

FPV in combination with efavirenz (EFV) (adults):

- Only FPV boosted with RTV should be used in combination with EFV.
- *Twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily.
- *PI-naive patients only, once-daily regimen:* FPV 1400 mg + RTV 300 mg + EFV 600 mg, all once daily.

FPV in combination with maraviroc (MVC) (adults):

- See MVC section for dosing of FPV with MVC.

- APV is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.
- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

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, a patient's medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

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.
- *Pediatric specific:* In clinical trials of fosamprenavir, vomiting was more frequent in children than in adults (20%–60% vs. 10%–16%, respectively) as was neutropenia (15% vs. 3%, respectively).[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/APV_FPV.html).

Pediatric Use: Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but the Panel recommends use only for children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this or any other age group because of low exposures and because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.[2]

Dosing recommendations for fosamprenavir are based on 3 pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In 2 open-label trials in both treatment-experienced and treatment-naive children from ages 2 to 18 years;[3, 4] fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.[1] Exposures in those younger than age 6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir. Given these low exposures, limited data, large volumes, unpleasant taste, and the availability of alternatives for infants and young children, the panel does not recommend fosamprenavir use in infants younger than 6 months.

Population	Dose	AUC_{0-24} (mcg*hr/mL) except where noted	C_{min} (mcg/mL)
Infants <6 months	45 mg FPV/10 mg RTV per kg twice daily	26.6[a]	0.86
Children aged 2–<6 years	30 mg FPV per kg twice daily (no RTV)	22.3[a]	0.513
Children weighing <11 kg	45 mg FPV/7 mg RTV per kg twice daily	57.3	1.65
Children weighing 15–<20 kg	23 mg FPV/3 mg RTV per kg twice daily	121.0	3.56
Children weighing ≥20 kg	18 mg FPV/3 mg RTV per kg twice daily (max 700/100)	72.3–97.9	1.98–2.54
Adults	1400 mg FPV twice daily (no RTV)	33	0.35
Adults	1400 mg FPV/100–200 mg RTV once daily	66.4–69.4	0.86–1.45
Adults	700 mg FPV/100 mg RTV twice daily	79.2	2.12

[a] AUC_{0-12} (mcg*hr/mL)

Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies, therefore, area under the curve and C_{min} are not available.

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Indinavir (IDV, Crixivan) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 because of the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

- Not approved for use in children.
- A range of IDV doses (234–500 mg/m^2 of body surface area) boosted by low-dose ritonavir (RTV) have been studied in children (see text).

Adolescent/adult dose:

- 800 mg IDV + 100 or 200 mg RTV every 12 hours

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- 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

- When given in combination with RTV, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If co-administered with didanosine (ddI), give IDV and ddI ≥1 hour apart on an empty stomach.
- IDV capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- Dosing in patients with hepatic impairment: 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:* CYP3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

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.
- *Less common (more severe):* Fat maldistribution.
- *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).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

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 Use: Indinavir has not been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.[1]

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that an unboosted indinavir dose of 500 to 600 mg/m^2 of body surface area given every 8 hours results in peak blood concentrations and area under the curve slightly higher than those in adults but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.[2-5] Studies in small groups of children of a range of ritonavir-boosted indinavir doses have shown that indinavir 500 mg/m^2 of body surface area plus ritonavir 100 mg/m^2 of body surface area twice daily is probably too high,[6] that indinavir 234 to 250 mg/m^2 of body surface area plus low-dose ritonavir twice daily is too low,[7, 8] and that indinavir 400 mg/m^2 of body surface area plus ritonavir 100 to 125 mg/m^2 of body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable interindividual variability and high rates of toxicity.[8-10]

As noted above, the cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%).[11] This is likely due to the difficulty in maintaining adequate hydration in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219 demonstrated a hazard ratio of 1.7 for risk of renal dysfunction in children receiving antiretroviral therapy with indinavir.[12]

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated November 1, 2012; last reviewed November 1, 2012)

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/per mL (contains 42.4% alcohol by volume)

Film-coated tablets: 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

Dosing Recommendations

Neonatal dose (<14 days):

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days.

Dosing for individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV)

Infant dose (14 days–12 months):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r per m^2 of body surface area twice daily.

  NOTE: Use of 300 mg/75 mg LPV/r per m^2 of body surface area in infants aged 12 months or younger is associated with lower LPV trough levels than those found in adults; in infants, LPV dosing should be adjusted for growth at frequent intervals (see text below).

Pediatric dose (>12 months–18 years):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily is routinely used by many clinicians, especially for patients previously treated with antiretroviral drugs or when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing (see text below).
- 230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients older than age 1 year. For patients already receiving LPV/r, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to "grow

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsade de pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see *Major Toxicities* below).

Special Instructions

- LPV/r tablets can be administered without regard to food; 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, as a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see *Pediatric Use*).
- LPV/r oral solution can be kept at room temperature up to 77°F (25°C) if used within 2 months. If kept refrigerated (2° to 8°C or 36° to 46°F) LPV/r oral solution remains stable until the expiration date printed on the label.

into" the 230 mg/m^2 dosage as they gain weight over time (see text below). Some would continue the infant dose (300 mg/m^2 of body surface area per dose twice daily) while on LPV/r liquid formulation.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents

	Recommended number of 100 mg/25 mg LPV/r Tablets Given Twice Daily	
Dosing target	300 mg/m^2/dose given twice daily	230 mg/m^2/dose given twice daily
Body Weight (kg)		
15–20 kg	2	2
>20–25 kg	3	2
>25–30 kg	3	3
>30–35 kg	4[a]	3
>35–45 kg	4	4
>45 kg	4 or 5[b]	4

[a] Note that 4 of the 100 mg/25 mg LPV/r tablets can be substituted by 2 tablets each containing 200 mg/50 mg LPV/r, but the 200 mg/50 mg LPV/r tablets are bigger and may be difficult to swallow

[b] ***In patients receiving concomitant NVP, EFV, FPV, or NFV***, for body weight >45 kg, the FDA-approved adult dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one tablet of 100 mg/25 mg LPV/r. Some Panel members would use 600 mg/150 mg LPV/r for ease of dosing.

Adult dose (>18 years):

- 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, or in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV, or in patients with three or more LPV-associated mutations (see *Special Instructions* for list):

***In patients with three or more LPV-associated mutations* (see *Special Instructions* for list):**

- The panel generally does not recommend once-daily dosing of LPV/r for children aged <18 years because of high variability of its metabolism in children.
- Do not use once daily if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P (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 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 ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

- 400 mg/100 mg LPV/r twice daily.

Dosing 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.)*

- Once-daily dosing should **not** be used.

Pediatric dose (>12 months to 18 years):

- 300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult dose (>18 years):

- Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one 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:* CYP450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. Fluticasone, a commonly used inhaled and intranasal steroid, should not be used in patients treated with lopinavir/ritonavir.

Major Toxicities:

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia
- *Less common (more severe):* Fat maldistribution
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases). 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 an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency,[1] life-threatening bradyarrhythmias and cardiac dysfunction,[2-4] and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression.[4] These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%.[4] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir.[1]

Resistance: The International Antiviral 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 Use:

Lopinavir/ritonavir is FDA-approved for use in children. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

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 m^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 dose that is directly scaled for body surface area.

A PK study in 12 children aged 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).[5] For 15 children ages 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.[5] In a study of 23 children (median age 5.6 years; range 0.4 to 13 years) treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), mean lopinavir area under the curve (AUC) and C_{min} were lower than that observed in adults treated with 400/100 mg lopinavir/ritonavir twice daily.[6] Lopinavir C_{min} <1.0 mg/L was found in 7 of 23 participants: 5 of 7 in the age group <2 years, and 2 of 16 children aged 2 years or older ($P = 0.01$).[6] Therefore, some clinicians choose to initiate therapy in children ages 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.

The PK 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 age 6 weeks[7] and infants aged 6 weeks to 6 months.[8] Lopinavir exposures from these studies are compared to those in older children[5] and adults[9] as shown in the table below. Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

	Adults[9]	Children[5]	Children[5]	Infants at 12 months[10] [a]	Infants 6 weeks–6 months[8]	Infants <6 weeks[7]
N	19	12	15	20	18	9
Dose LPV	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC mcg-hr/mL	92.6	72.6	116.0	101.0	74.5	43.4
C_{max} mcg/mL	9.8	8.2	12.5	12.1	9.4	5.2
C_{trough} mcg/mL	7.1	4.7	7.9	4.9	2.7	2.5
C_{min} mcg/mL	5.5	3.4	6.5	3.8	2.0	1.4

[a] Data generated in study cited but not reported in final manuscript; data in table according to an e-mail from Edmund Capparelli, PharmD (April 18, 2012)

Even at this higher dose, pre-dose (C_{trough}) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants aged 6 weeks or younger compared with those ages 6 weeks to 6 months. By age 12 months, lopinavir AUC was similar to that found in older children.[10] Because infants gain weight rapidly in the first months of life, one important way to optimize lopinavir dosing is to weigh a patient and adjust the dose for growth at frequent intervals. Given the safety of doses as high as 400 mg/m^2 body surface area in older children and adolescents,[11] 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.

In both children and adults the lopinavir C_{trough} is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors or concomitant fosamprenavir or nelfinavir and 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.[5] 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.[5, 6] In a study of 15 HIV-infected children 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 inter-individual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.[12] A PK study in 20 children aged 10 to 16 years 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.[13]

Once-daily dosing of lopinavir/ritonavir 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV infection in therapy-naive adults older than age 18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM) because of high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21 (35.6%) of 59 patients.[14-17] Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower

variability in trough levels,[17, 18] but the Panel remains concerned about the long-term effectiveness of once-daily lopinavir/ritonavir in children.

Lopinavir/ritonavir has been shown to be effective as salvage therapy in HIV-infected children with severe immune suppression,[19, 20] although patients with greater prior exposure to antiretrovirals may have slower reductions in virus load to undetectable concentrations[20, 21] and less robust response in CD4 percentage.[22] Twice daily doses of lopinavir used in this cohort were 230 to 300 mg/m^2 of body surface area in 39% of patients, 300 to 400 mg/m^2 of body surface area in 35%, and greater than 400 mg/m^2 of body surface area per dose in 4%.[22]

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just before 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 (IQ), and in both adults and children treated with lopinavir/ritonavir, virus load reduction is more closely associated with IQ than with either the C_{trough} or EC_{50} alone.[23-26] A study of the practical application of the IQ 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 fosamprenavir, nelfinavir, 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).[11] Results of a modeling study suggest that standard doses of lopinavir/ritonavir are likely to be inadequate for treatment-experienced children and underscore the potential utility of TDM in children previously treated with protease inhibitors and now on salvage therapy with lopinavir/ritonavir.[27]

Lopinavir/ritonavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C_{max}, and C_{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.[28] In a PK study using a generic adult formulation of lopinavir/ritonavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C_{trough} measurements.[18]

Compared with children treated with NNRTI-based regimens, those treated with lopinavir/ritonavir may have less robust weight gain and smaller increases in CD4 percentage.[29-31] The poor weight gain associated with lopinavir/ritonavir is not understood.

The poor palatability of the oral solution can be a significant challenge to medication adherence for some children and families. Numbing of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods, chocolate syrup, or peanut butter, for example, or by flavoring the solution by the pharmacist prior to dispensing, are examples of interventions that may improve tolerability.

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Nelfinavir (NFV, Viracept) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/infant dose:

- NFV should not be used for treatment in children aged <2 years.

Pediatric dose (2–13 years of age):

- 45–55 mg/kg twice daily.

Adolescent/adult dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice 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 NFV with meal or light snack.
- If co-administered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- Patients unable to swallow NFV tablets can dissolve the tablets in a small amount of water. Once tablets are 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 or other nonacidic foods.

Metabolism

- CYP2C19 and 3A4 substrate.
- Metabolized to active M8 metabolite.
- CYP3A4 inhibitor.

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

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, ritonavir boosting does not significantly increase nelfinavir concentrations and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.

- Before administering nelfinavir, carefully review a patient's medication profile 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 Antiviral 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 Use: Nelfinavir is a protease inhibitor (PI) that has been used in combination with 2 nucleoside reverse transcriptase inhibitors in children aged >2 years. Nelfinavir is not recommended for treatment in children aged <2 years (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 for prevention of mother-to-child transmission of HIV*).

Nelfinavir in combination with other antiretroviral drugs has been extensively studied in HIV-infected children.[1-8] In randomized trials of children ages 2 to 13 years receiving nelfinavir as part of triple antiretroviral therapy (ART), the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior history of ART, the number of drugs included in the combination regimen, and dose of nelfinavir used. The relatively poor ability of nelfinavir to control plasma viremia in infants and children may be related in part to the ARV's reduced potency compared with other PIs or non-nucleoside reverse transcriptase inhibitors as well as highly variable drug exposure, metabolism, and poor patient acceptance of available formulations.[9-11]

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increased by as much as five fold) and decreases pharmacokinetic (PK) variability relative to the fasted state. Drug exposure may be even more unpredictable in pediatric patients than in adults because of increased clearance of nelfinavir observed in children, and difficulties in taking nelfinavir with sufficient food to improve bioavailability. A pediatric powder formulation, no longer available, was poorly tolerated when mixed with food or formula. In the PENTA-7 trial, 35% (7 of 20) of infants started on powder at initiation of therapy were switched from the powder to crushed tablets because of difficulty administering the oral formulation to the infants.[1] A slurry made by dissolving nelfinavir tablets in water or other liquids can be administered to children who are unable to swallow tablets. The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.[12]

Nelfinavir is metabolized by multiple CYP-450 enzymes including CYP3A4 and CYP2C19. M8, the major oxidative metabolite, has *in vitro* antiviral activity comparable to the parent drug. The variability of drug exposure at any given dose is much higher for children than adults,[13] which has been attributed at least in part to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children.[14, 15] Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir PKs and the virologic responses to combination therapy in HIV-1-infected children. These findings

suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in HIV-1-infected children.[9]

Antiviral response to nelfinavir is significantly less in children younger than age 2 years than in older children.[6, 8, 16] 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.[17, 18] For these reasons, nelfinavir is not recommended for use in children younger than 2 years of age. In older children and adolescents, it is unclear when to change from the recommended 45 to 55 mg/kg twice-daily dose to the adult dose of 1250 mg twice daily. Doses higher than those recommended in adults may be required in some patients.

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{min}) <1.0 mcg/mL.[19-21] In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of children 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.[22] 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.[22] Therapeutic drug monitoring (TDM) of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir.[19, 23] Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of TDM and appropriate dose adjustment may be even greater for children. Better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing.[15, 24]

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Ritonavir (RTV, Norvir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Oral solution (contains 43% alcohol by volume): 80 mg/mL

Capsules: 100 mg

Tablets: 100 mg

Dosing Recommendations

RTV as a pharmacokinetic (PK) enhancer:
The major use of RTV is as a PK enhancer of other protease inhibitors used in pediatric patients and in adolescents and adults. The dose of RTV recommended varies and is specific to the drug combination selected. See dosing information for specific protease inhibitors (PIs).

In the unusual situation when RTV is prescribed as sole PI:

- See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (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
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

Special Instructions

- Administer RTV with food to increase absorption and reduce GI side effects.
- If RTV is prescribed with didanosine (ddI), administer the drugs 2 hours apart.
- Refrigerate RTV capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). RTV tablets are heat stable.
- Do not refrigerate RTV oral solution; store at room temperature (68–77°F or 20–25°C). Shake the solution well before use.
- RTV oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is smaller than the capsule and thus easier to swallow.

To increase tolerability of RTV oral solution in children:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
- Before administration, give a child ice chips, a popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.
- After administration, give a child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P (CYP)3A4 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. Data are unavailable on RTV dosing for 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 with ritonavir.
- Before ritonavir is administered, a patient's medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.
- Avoid concomitant use of intranasal or inhaled fluticasone. Use caution when prescribing ritonavir with other inhaled steroids because of reports of adrenal insufficiency.[1-3]

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, 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.

Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[4]

Resistance: Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs).

Pediatric Use: Ritonavir has been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Use of ritonavir as the sole PI in antiretroviral therapy (ART) in children is not recommended. However, in both children and adults, ritonavir is recommended as a PK enhancer to boost another/second PI in an ART regimen. Ritonavir acts by inhibiting the metabolism of the second (boosted) PI in the regimen, thereby increasing the plasma concentration of the second/boosted PI. Lopinavir/ritonavir, a PI coformulation, has been well studied in children and is a preferred PI for therapy in children (see Lopinavir/Ritonavir). Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, and atazanavir are available (see individual PIs for more specific information).

Although ritonavir has been well studied, its use in children as a sole PI for therapy is limited because ritonavir is associated with a higher incidence of GI toxicity and has a greater potential for drug-drug interactions than other PIs. Also, ritonavir as a sole PI is associated with a higher risk of virologic failure than efavirenz or lopinavir/ritonavir.[5-7] In addition, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules or tablets twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than 2 years, and doses of 350 to 450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group.[8-19]

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.[4] Potentially life-threatening arrhythmias in premature newborn infants treated with lopinavir/ritonavir have been reported; thus, lopinavir/ritonavir should not be used in this group of patients.[20, 21] Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as those with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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Saquinavir (SQV, Invirase) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Hard-gel capsules: 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):

Aged <2 years:

- No dose has been determined.

Aged ≥2 years (conditional dosing based on limited data, see text):

Weight (kg)	Dose SQV + RTV
5–<15 kg	SQV 50 mg/kg + RTV 3 mg/kg, both twice daily
15–40 kg	SQV 50 mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50 mg/kg + RTV 100 mg, both twice daily

Aged ≥7 years in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (conditional dosing based on limited data, see text):

- SQV 750 mg/m^2 (max 1600 mg) or SQV 50 mg/kg have been used in combination with LPV/r, both twice daily.

Adolescent (aged ≥16 years)/adult dose:

SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

- SQV 1000 mg + RTV 100 mg, both twice daily.
- SQV 1000 mg + LPV/r 400/100 mg, both twice daily.

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and ventricular tachycardia (torsades de pointes) have been reported.

Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: Use with caution.

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

- *Metabolism:* Saquinavir is both a substrate and inhibitor of the CYP3A4 system, and there is potential for numerous drug interactions.
- Before administration, a 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 Use: Saquinavir is not Food and Drug Administration (FDA)-approved for use in children. Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors (PIs) in HIV-infected children.[1-6] Initial studies suggest that saquinavir should not be used without boosting by ritonavir or lopinavir/ritonavir. A pharmacokinetic (PK) analysis of 5 children aged younger than 2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir demonstrated that drug exposure was lower in children younger than age 2 years whereas drug exposure was adequate in those ages 2 to 5 years.[7] For this reason, saquinavir should not be given to children younger than age 2 years until an appropriate dose is identified. In children aged ≥2 years, a dose of 50 mg/kg twice daily (maximum dose = 1000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 – <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 – 40 kg) resulted in area under the curve and steady state trough concentration (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 for salvage therapy in children.[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 1600 mg) to a regimen containing lopinavir/ritonavir dosed at 400/100 mg/m^2 of body surface area twice daily (for patients not concurrently taking a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or lopinavir/ritonavir 480/120 mg/m^2 of body surface area twice daily for patients concurrently administered an NNRTI, 18 subjects (median age 14.2 years, range 7.7–17.6 years) were enrolled. The addition of saquinavir at these doses was well tolerated and did not appear to alter lopinavir PKs. Saquinavir dosing was adjusted in four patients (decreased in three, increased in one).[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 of body surface area and lopinavir/ritonavir was dosed at 230/57.5 mg/m^2 of body surface area, 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 minimum plasma concentration (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% (8 mg/kg). Median total cholesterol and high-density lipoprotein values increased significantly through 96 weeks from 144 to 196 mg/dL and from 44 to 57 mg/dL, respectively.[8, 9]

In a healthy adult volunteer study, saquinavir/ritonavir use was associated with increases in both QT and PR intervals.[11] The degree of QT prolongation was greater than that seen with some other boosted PIs. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Saquinavir/ritonavir is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An electrocardiogram is recommended before initiation of therapy with saquinavir and should be considered during therapy.

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Tipranavir (TPV, APTIVUS) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 International Units (IU) vitamin E/mL

Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose used for TPV is higher than that used for other protease inhibitors (PIs).

Pediatric dose (aged <2 years):

- Not approved for use in children aged <2 years.

Pediatric dose (2–18 years of age):

Not recommended for treatment-naive patients.

- *Body surface area dosing:*
  TPV 375 mg/m^2 + RTV 150 mg/m^2, 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:

Not recommended for treatment-naive patients.

- TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily.

Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia.

Special Instructions

- Administer TPV and RTV together with food.
- TPV oral solution contains 116 IU vitamin E/mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- TPV contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- Store TPV oral solution at room temperature 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store unopened bottles of oral TPV capsules in a refrigerator at 2° to 8°C (36°–46°F). Once bottle is opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.
- 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.

- Use of TPV is contraindicated in patients with moderate or severe hepatic impairment.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate.
- Dosing in patients with renal impairment: No dose adjustment required.
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

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

- Tipranavir has the potential for multiple drug interactions.
- Before tipranavir is administrated, a patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients 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. Elevated transaminases, cholesterol, and triglycerides.
- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis 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. Increased risk of intracranial hemorrhage.

Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

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 Use: Tipranavir is Food and Drug Administration (FDA) approved for use in children aged ≥2 years who are treatment-experienced and infected with HIV strains resistant to more than one protease inhibitor (PI).[1] The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the burden of taking a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events that limit its use to patients with few treatment options. However, tipranavir is approved for use in children as young as age 2 years and is available in a liquid formulation.

FDA approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of tipranavir/ritonavir in HIV-infected children (PACTG 1051/BI-1182.14).[2] This study enrolled treatment-experienced children (with the exception of 3 treatment-naive patients) ages 2 to 18 years (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children in 3 age strata were randomized to 2 different doses of tipranavir/ritonavir: tipranavir/ritonavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg/m^2 body surface area (high dose, 57 patients) twice daily, plus optimized background therapy. All children initially received the oral solution but patients who were aged 12 years or older and receiving the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily were eligible to switch to tipranavir capsules after Week 4. At baseline, resistance to all commercially available PIs was present in greater than 50% of patient isolates, and the tipranavir/ritonavir mutation scores increased with age.[2] At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of those receiving the high dose had viral loads <400 copies/mL. The groups did not differ in percentage of patients who achieved viral loads <50 copies/mL. The proportion of patients with HIV RNA levels <400 copies/mL tended to be greater in the youngest patients (70%) who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 T lymphocyte count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, adverse 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 because of adverse events. The most common adverse events were gastrointestinal disturbances; 37% of participants had vomiting and 24% had diarrhea. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase and creatine phosphokinase) was seen in 11% of children. Four patients (all in the low-dose group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus high-dose group reached statistical significance ($P = 0.04$). In a multivariate model, three variables (listed in order) predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100,000 copies/mL. GIQ is calculated by dividing the tipranavir trough concentration by the number of tipranavir resistance-conferring mutations genotyped from a patient's HIV strain. 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, high-dose tipranavir/ritonavir has been recommended.

PKs of the liquid formulation at steady state were assessed.[3] In children ages 2 to <12 years, at a dosage of tipranavir/ritonavir 290/115 mg/m^2 body surface area, tipranavir trough concentrations were consistent with those achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children ages 12 to 18 years 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 PK analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age.[3] Based on these studies, the final dose of tipranavir/ritonavir 375/150 mg/m^2 body surface area twice daily is recommended.

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir/mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/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. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%).[2] Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.[4]

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Appendix A: Pediatric Antiretroviral Drug Information

Entry and Fusion Inhibitors

Enfuvirtide (ENF, T-20, Fuzeon)

Maraviroc (MVC, Selzentry)

Enfuvirtide (ENF, T-20, Fuzeon) (Last updated August 11, 2011; last reviewed November 1, 2012)

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

Dosing Recommendations

Pediatric/adolescent dose (aged 6–16 years):

- *Children aged <6 years:*
  Not approved for use in children aged <6 years.
- *Children aged ≥6 years:*
  2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Adolescent (aged >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 rate of bacterial pneumonia (unclear association).
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous (SQ) 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.
- ENF must be given SQ; severity of reactions increases 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 an HSR; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with an HSR.

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 with enfuvirtide.

Major Toxicities:

- *More common:* Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are 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).
- *Rare:* Hypersensitivity reactions (HSRs) (<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 HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.
- *Pediatric specific:* Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).[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/ENF.html).

Pediatric Use: Although enfuvirtide is Food and Drug Administration (FDA) approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens[2] has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

A single-dose pharmacokinetic (PK) evaluation study of enfuvirtide given SQ to 14 HIV-infected children aged 4 to 12 years (PACTG 1005) identified that enfuvirtide 60 mg/m^2 of body surface area per dose resulted in a target trough concentration that approximated the "equivalent" of a 90-mg dose delivered SQ

to an adult (1,000 mg/mL).[3] In a second pediatric study of 25 children aged 5 to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily yielded drug concentrations similar to 60 mg/m^2 of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.[4] The FDA-recommended dose of enfuvirtide for children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m^2 per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a >1.0 log reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively.[5] However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at Week 96. Most children had local injection site reactions.[6] 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 SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and increase in CD4 T lymphocyte (CD4 cell) count was 106 cells/mm^3 (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm^3 in children and 84 cells/mm^3 in adolescents. Local skin reactions were common in all age groups (87% of study participants). 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 in some studies (FDA) but not in others.[7] Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.

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Maraviroc (MVC, Selzentry) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 aged <16 years.
- A pediatric clinical trial is under way

Adolescent (aged >16 years)/adult dose:

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (PIs) (except tipranavir/ritonavir [TPV/r])	150 mg twice daily
When given with nucleoside reverse transcriptase inhibitors (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 potent CYP3A inhibitor)	600 mg twice daily

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Orthostatic hypotension (especially in patients with severe renal insufficiency)

Special Instructions

- Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in the main body of the guidelines) before using MVC to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use MVC in patients with only CCR5-tropic virus. Do not use if CXCR4 or mixed/dual-tropic HIV is present.
- MVC 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 3A4 (CYP3A4) substrate
- Dosing of MVC in patients with hepatic impairment:

  Use caution when administering MVC to patients with hepatic impairment. Because MVC is metabolized by the liver,

concentrations in patients with hepatic impairment may be increased.

- Do not use MVC in patients with creatinine clearance (CrCl) <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.
- Dosing of MVC in patients with renal impairment:

  Refer to the manufacturer's prescribing information

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 CYP3A4 and p-glycoprotein (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with maraviroc.

Major Toxicities:

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.
- *Less common (more severe):* Hepatotoxicity that may be preceded by evidence of a systemic allergic reaction (such as pruritic rash, eosinophilia or elevated immunoglobulin [IgE]) has been reported. Serious adverse events occurred in less than 2% of maraviroc-treated adult patients and included cardiovascular abnormalities (such as 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 Use: The pharmacokinetics (PK), safety, and efficacy of maraviroc in patients aged <16 years have not been established. A dose-finding study is under way in children aged 2 to 17 years.[1] In this trial, maraviroc dose is based upon body surface area and the presence or absence of a potent CYP3A4 inhibitor in the background regimen. Preliminary PK data are encouraging in those on a potent CYP3A4 inhibitor, but exposures are very low in those not on a potent CYP3A4 inhibitor.

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Appendix A: Pediatric Antiretroviral Drug Information

Integrase Inhibitors

Raltegravir (RAL, Isentress)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress) (Last updated November 5, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets*: 400 mg (film-coated poloxamer tablet)

Chewable Tablets: 100 mg (scored) and 25 mg
* Film-coated tablets and chewable tablets are not interchangeable.

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

Children aged 2 to <12 years:

- <25 kg: Chewable tablet twice daily to maximum of 300 mg twice daily (see table)
- ≥25 kg: 400 mg film-coated tablet twice daily OR chewable tablets (see table)

Dosing of chewable tablets in children aged 2 to <12 years of age

Body Weight (kg)	Dose	Number of Chewable Tablets
10 to <14	75 mg twice daily	3 X 25 mg twice daily
14 to <20	100 mg twice daily	1 X 100 mg twice daily
20 to <28	150 mg twice daily	1.5 X 100 mg twice daily
28 to <40	200 mg twice daily	2 X 100 mg twice daily
≥40	300 mg twice daily	3 X 100 mg twice daily

Adolescent (≥12 years of age)/adult dose:

- 400 mg film-coated tablet twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.
- Film-coated tablets and chewable tablets are not interchangeable. Chewable tablets have better bioavailability than the film-coated tablets. Chewable tablets should be stored in the original package with desiccant to protect from moisture.

Metabolism

- Uridine diphosphate glucotransferase (UGT1A1)-mediated glucuronidation.
- Dosing of RAL 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 RAL in patients with renal impairment: No dosage adjustment necessary.

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

- *Metabolism:* The major route of raltegravir elimination is mediated through glucuronidation by UGT1A1.
- Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Efavirenz and etravirine may decrease raltegravir concentrations.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting, insomnia. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than are patients who are 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 including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis 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 Use: Raltegravir is approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years. Raltegravir has been studied in 126 antiretroviral (ARV) treatment-experienced HIV-1-infected children and adolescents aged 2 to 18 years in combination with an optimized background ARV regimen in IMPAACT P1066. Additional experience from the French expanded access program in treatment-experienced adolescents support the good virologic and immunologic results observed in P1066.[1, 2]

IMPAACT P1066 is a Phase I/II open label multicenter study to evaluate the pharmacokinetic (PK) profile, safety, tolerability, and efficacy of various formulations of raltegravir in HIV-infected children. Subjects received either the 400-mg film-coated tablet formulation twice daily (patients aged 6–18 years and weighing at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). Current pediatric approval and dosing recommendations are based upon these evaluations in 96 patients.[3-7]

In IMPAACT P1066, the initial dose-finding stage includes intensive PK evaluation in various age cohorts: (aged 12 to <19 years, 6 to <12 years, 2 to <6 years). Dose selection was based upon achieving target PK parameters similar to those seen in adults: PK targets are geometric mean (GM) area under the curve of 14-25 μMxh and GM 12 h concentration >33 nM. Additional subjects were then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. Ninety-three (97%) subjects completed 24 weeks of treatment with 54% achieving HIV RNA <50 copies/mL with a mean CD4 T lymphocyte count (percent

[%]) increase of 119 cells/mm^3 (3.8%). The frequency, type, and severity of drug-related adverse reactions through week 24 were comparable to those observed in adult studies. Observed adverse reactions considered drug-related included one patient with grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient with a grade 2 allergic rash; and one patient with grade 3 ALT and grade 4 AST laboratory elevations.

The investigational raltegravir oral granules for suspension formulation are currently under study in P1066 in children aged 4 weeks to <2 years. Recent data, obtained from 9 children aged 6 months to <2 years, suggest that the oral granules are well tolerated with favorable preliminary efficacy. PK data obtained in 8 of the 9 young children achieved targets similar to those observed in the 2- to 11-year-olds receiving the chewable tablets.[8] A dosage of 6 mg/kg every 12 hours was chosen for continued study in this age group.

The raltegravir chewable tablet has higher oral bioavailability than the film-coated tablet based on a comparative study in healthy adult volunteers.[9] In the PK of raltegravir, interpatient and intrapatient variability is considerable.[10]

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Elvitegravir (EVG) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Only available in fixed-dose combination tablets (Stribild):

Elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF)

EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg

Dosing Recommendations

Pediatric dose (aged <18 years):

- Not FDA-approved or -recommended for use in children aged <18 years.

Adult dose (aged ≥18 years):

- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

Selected Adverse Events

- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD)

Special Instructions

- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; in patients at risk of renal impairment, also monitor serum phosphate. Patients with increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

Metabolism

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

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

- *Metabolism:* Stribild contains elvitegravir and cobicistat. Elvitegravir is metabolized by cytochrome P (CYP) 3A4 and is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, it inhibits ATP-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided.
- *Protease inhibitors (PIs):* Stribild should not be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A.
- Not recommended for use with other ARV drugs.

Major Toxicities:

- *More common:* Nausea, diarrhea, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors including tenofovir disoproxil fumarate (tenofovir) and emtricitabine. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been reported in both adults and children taking tenofovir; 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 Antiviral 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/DR/).

Pediatric Use: Elvitegravir is only available as the fixed-dose combination product Stribild, which contains elvitegravir/cobicistat/emtricitabine/tenofovir. Stribild is not U.S. Food and Drug Administration (FDA)-approved for use in children aged <18 years. There are no data on its use in individuals aged <18 years.

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor added as a pharmacokinetic enhancer. Cobicistat slows elvitegravir metabolism and allows once-daily administration of the combination. Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years[1] based on trials showing non-inferiority to regimens of emtricitabine/tenofovir plus atazanavir/ritonavir,[2] or emtricitabine/tenofovir plus efavirenz.[3] There is cross-resistance between elvitegravir and raltegravir.[4] Cobicistat alters the renal tubular secretion of creatinine, so creatinine-based calculations of estimated glomerular filtration rate will be altered, even though the actual glomerular filtration rate might be only minimally changed.[5] Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal toxicity.[1]

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Appendix B: Acronyms (Last updated November 1, 2012; last reviewed November 1, 2012)

3TC	lamivudine
AAP	American Academy of Pediatrics
ABC	abacavir
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AUC	area under the curve
AV	atrioventricular
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
cART	combination antiretroviral therapy
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CHER Trial	The Children with HIV Early Antiretroviral Therapy Trial
CHIPS	Collaborative HIV Pediatric Study
CK	creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
COBI	cobicistat
CPK	creatine phosphokinase
CrCl	creatinine clearance
CT	computed tomography continuous therapy
CVD	cardiovascular disease
CYP	cytochrome P

d4T	stavudine
ddI	didanosine
DM	diabetes mellitus
D/M	dual-mixed (tropic)
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy
DRESS	drug rash with eosinophilia and systemic symptoms
DRV	darunavir
DXA	dual-energy x-ray absorptiometry
EBV	Epstein-Barr virus
EC	enteric-coated
ECG	electrocardiogram
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
EM	erythema multiforme
ENV	enfuvirtide
ETR	etravirine
EVG	elvitegravir
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FPV	fosamprenavir
FTC	emtricitabine
FXB	François-Xavier Bagnoud Center
G6PD	glucose-6-phosphate dehydrogenase
G-CSF	granulocyte colony-stimulating factor
GGT	gamma glutamyl transpeptidase
GI	gastrointestinal
GIQ	genotypic inhibitory quotient
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol

Hgb	hemoglobin
HHS	U.S. Department of Health and Human Services
HIVMA	HIV Medicine Association
HPPMCS	HIV Paediatric Prognostic Markers Collaborative Study
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IAS-USA	International Antiviral Society-USA
IC_{50}	mean inhibitory concentration
ICH	intracranial hemorrhage
IDSA	Infectious Diseases Society of America
IDV	indinavir
IFA assay	immunofluorescent antibody assay
IgE	immunoglobulin E
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRIS	immune reconstitution inflammatory syndrome
IU	international units
IUD	intrauterine device
IV	intravenous/intravenously
IVIG	intravenous immune globulin
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LIP	lymphoid interstitial pneumonia
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MAC	*Mycobacterium avium* complex
m-DOT	modified directly observed therapy
MEMS	Medication Event Monitoring System
MRI	magnetic resonance imaging
msec	milliseconds
MTCT	mother-to-child transmission
MVC	maraviroc

NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor
NVP	nevirapine
OARAC	Office of AIDS Research Advisory Council
OBR	optimized background regimen
OBT	optimized background therapy
OGTT	oral glucose tolerance test
OI	opportunistic infection
PBMC	peripheral blood mononuclear cells
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PENTA	Paediatric European Network for Treatment of AIDS
PG	plasma glucose
Pgp	p-glycoprotein
PI	protease inhibitor
PIDS	Pediatric Infectious Diseases Society
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PPI	proton-pump inhibitor
PR	protease
PUFA	polyunsaturated fatty acid
RAL	raltegravir
RBV	ribavirin
RPG	random plasma glucose
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SJS	Stevens-Johnson syndrome
SQ	subcutaneous
SQV	saquinavir

STI	structured treatment interruptions
T-20	enfuvirtide
TB	tuberculosis
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis
TG	triglyceride
THAM	tris–hydroxymethyl-aminomethane
TMP-SMX	trimethoprim sulfamethoxazole
TPV	tipranavir
TPV/r	tipranavir/ritonavir
UA	urinalysis
UGT1A1	uridine diphosphate glucoronosyltransferase
ULN	upper limit of normal
USPHS	U.S. Public Health Service
WHO	World Health Organization
ZDV	zidovudine