Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

August 11, 2011

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

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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.

access mobile site

What's New in the Pediatric Guidelines?

Key changes made to update the August 16, 2010, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* are summarized below. All of the changes are highlighted in the guidelines. Throughout the document, references have been updated to include new publications where relevant.

When to Start Antiretroviral Therapy

Antiretroviral-naive HIV-infected infants 12 months or younger

- Antiretroviral therapy (ART) continues to be recommended for all infants younger than 12 months of age regardless of clinical, immunologic, or virologic symptoms. The Panel believes that although it is important to assess, discuss, and address issues associated with adherence with the infant's caregivers, it is very important to expedite this assessment for young infants given the high risk of disease progression and mortality in young HIV-infected infants.

Antiretroviral-naive HIV-infected children 1 year or older

- Current adult ART guidelines are discussed, along with similarities and differences between guidelines for children and adults. The CD4 threshold for recommending ART in children ages ≥5 years with minimal or no clinical symptoms has been increased from <350 cells/mm^3 to <500 cells/mm^3.
    - The evidence for this recommendation is strongest for children with CD4 counts <350 cells/mm^3 **(AI*)**.
    - For children with CD4 counts 350–500 cells/mm^3 **(BII*)**, the recommendation is based on observational data in adults; hence the evidence base is not as strong. The Panel's recommendations should not prohibit research studies in children designed to answer this question more definitively.
- Treatment is also recommended for children with minimal or no clinical symptoms and normal immune status (CD4 percentage >25% if age 1 to <5 years, or CD4 count >500 cells/mm^3 if age ≥5 years) if plasma HIV RNA is >100,000 copies/mL **(BII*)**.
- Treatment may be considered for children age ≥1 year with normal immune status (CD4 percentage >25% if age 1 to <5 years, or CD4 count >500 cells/mm^3 if age ≥5 years) and plasma HIV RNA <100,000 copies/mL **(CIII)**.
- Because of slower disease progression among older children without symptoms of advanced disease, it is important to take time to educate both the caregiver and child about the need for adherence to the regimen and to resolve potential adherence problems before initiation of therapy. This is particularly true for children age ≥5 years given their lower risk of disease progression and the higher CD4 count threshold now recommended for initiating therapy.

What to Start

- The section has been reorganized to include a general discussion of factors to consider when selecting an initial antiretroviral (ARV) regimen for children and a specific discussion regarding the choice of a non-nucleoside reverse transcriptase inhibitor (NNRTI)- versus a protease inhibitor (PI)-

based initial regimen, citing recent results from pediatric clinical trials (PENPACT I [PENTA 9/PACTG 390] and P1060).

- The preferred initial therapy for all infants and children ages ≥14 days to <3 years is lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AI)**, with nevirapine-based regimens now considered an alternative regimen for initial therapy in this age group **(AI)**. Based on new data on toxicity in preterm infants, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.
- For initial therapy for children age >6 years, atazanavir with low-dose ritonavir boosting has been added as a second preferred PI choice **(AI*)**, joining lopinavir/ritonavir **(AI)**.
- Preferred dual-NRTI backbone regimens for initial therapy include abacavir plus lamivudine or emtricitabine in children age ≥3 months **(AI)**, tenofovir plus lamivudine or emtricitabine for adolescents age ≥12 years and Tanner Stage 4 or 5 **(AI*)**, or zidovudine plus lamivudine or emtricitabine at any age **(AI*)**.
- Two new alternative dual-NRTI backbone regimens for initial therapy have been added: didanosine plus lamivudine or emtricitabine at any age **(BI*)** or tenofovir plus lamivudine or emtricitabine for adolescents age ≥12 years and Tanner Stage 3 **(BI*)**.
- One new dual-NRTI backbone regimen for initial therapy in special circumstances has been added: tenofovir plus lamivudine or emtricitabine for adolescents age ≥12 years and Tanner Stage 2.
- Rilpivirine-containing regimens are currently not recommended for initial therapy in children because of lack of data on pediatric dosing and safety and lack of pediatric formulation.

Monitoring

- It is noted that temporary viral load elevations between the level of detection and 1,000 copies/mL ("blips") are often detected in adults and children on treatment and should not be considered viral failure.
- Urinalysis (UA) has been added as a recommended baseline laboratory evaluation, with re-evaluation every 6–12 months.

Toxicity

- New sections have been added to Table 17, Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations, on (1) central nervous system (CNS) toxicity, (2) gastrointestinal (GI) effects, (3) nephrotoxicity, and (4) peripheral nervous system toxicity. Existing sections have been updated.

Treatment Failure

- A new section discussing management of children with ongoing adherence problems as the reason for viral failure has been added. The use of lamivudine or emtricitabine alone as an interim "bridging regimen" in the special circumstance of children with treatment failure associated with drug resistance and persistent nonadherence is discussed.

Resistance Testing

- Phenotypic resistance testing (usually in addition to genotypic resistance testing) is recommended for patients with known or suspected complex drug resistance mutation patterns, which generally arise after viral failure of successive ARV regimens.
- Genotypic assays to detect mutations associated with CXCR4 or D/M tropic virus (Trofile-DNA) are discussed.

Pediatric Antiretroviral Drug Information

The section has been reorganized to improve readability. Updates with new pediatric data are provided when relevant for specific drugs.

- ***Abacavir:*** Once-daily abacavir dosing (16 mg/kg/day, maximum 600 mg once daily) may be considered in clinically stable children with undetectable viral load and stable CD4 count. A table comparing the steady-state pharmacokinetics (PKs) from five pediatric clinical trials of abacavir when dosed once or twice daily has been added.
- ***Lamivudine:*** Once-daily lamivudine (300 mg once daily) may be used for adolescents age ≥16 years who weigh ≥50 kg. A table comparing the steady-state PKs from three pediatric clinical trials of lamivudine when dosed once or twice daily has been added.
- ***Stavudine:*** Use of a lower dose of stavudine (30 mg twice daily regardless of weight) in adults and older adolescent is discussed.
- ***Tenofovir:*** An update on the effect of tenofovir on bone mineral density (BMD) and renal function in children has been added.
- ***Efavirenz:*** Interpatient variability in efavirenz exposure secondary to polymorphisms in cytochrome P (CYP)450 genes is discussed; therapeutic drug monitoring (TDM) can be considered for management of efavirenz-related toxicity.
- ***Etravirine:*** Pediatric investigational dosing for etravirine in children >6 years of age is discussed.
- ***Nevirapine:*** Extended-release nevirapine is newly available for adults but is not approved for use in children age <18 years because of lack of data in this age group.
- ***Rilpivirine:*** Drug information on rilpivirine is added; there are no pediatric data available at this time.
- ***Darunavir:*** Once-daily dosing of darunavir is not recommended for children age <12 years or any child age <18 years who is treatment experienced; once-daily dosing (darunavir 800 mg plus ritonavir 100 mg) may be considered for treatment-naive pediatric patients age 12–18 years who weigh >40 kg.
- ***Lopinavir/ritonavir:*** Due to cardiovascular toxicity observed in preterm infants, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.
- ***Saquinavir:*** Pretherapy electrocardiogram (ECG) is recommended for a patient initiating saquinavir-based therapy because significant PR and QT prolongation has been observed; saquinavir is not recommended for individuals with prolonged QT interval or those receiving other drugs that may prolong the QT interval.

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These updated *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the Francois-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).

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Introduction (Updated August 11, 2011)

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

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

Since the development of the initial guidelines in 1993 (with the support of the François-Xavier Bagnoud Center [FXBC], University of Medicine and Dentistry of New Jersey [http://www.fxbcenter.org]), dramatic advances in medical management have followed the results of clinical trials of ARV combination therapies in children. HIV mortality has decreased by more than 80%–90% since the introduction of protease inhibitor (PI)-containing combinations, and opportunistic and other related infections have significantly decreased in the era of highly active antiretroviral therapy (HAART)[3-9]. Advances including resistance testing and the ability to measure ARV drug levels have enabled clinicians to more carefully choose very effective initial regimens while preserving selected drugs and drug classes for second- or third-line regimens. Therapeutic strategies continue to focus on early initiation of ARV regimens capable of maximally suppressing viral replication to prevent disease progression, preserve immunologic function, and reduce the development of resistance. At the same time, availability of new drugs and drug formulations has led to regimens with less frequent dosing schedules that improve adherence. Improved monitoring and dosing schedules have also led to a decrease in drug failure due to toxicity. The use of ART during pregnancy in HIV-infected women has resulted in a dramatic decrease in the transmission rate to infants, which is currently less than 2% in the United States, and the number of infants with AIDS in the United States continues to decline[10-11]. Finally, children living with HIV infection are, as a group, growing older, bringing new challenges of adherence, drug resistance, reproductive health planning, management of multiple drugs, and long-term complications from HIV and its treatments.

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

- Acquisition of infection through perinatal exposure for most infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to zidovudine and other ARV drugs in most perinatally infected children;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- Age-specific differences in CD4 cell counts;
- Changes in pharmacokinetic (PK) parameters with age caused by the continuing development

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

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

Guidelines Development Process

An outline of the composition of the Panel and the guidelines development process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.
Panel members	The Panel is composed of approximately 25 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least 1 representative from each of the following Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected by the Panel after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found on the panel roster.
Financial disclosure	All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected infants, children, and adolescents
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	Described in Table 2.

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

Table 1. Outline of the Guidelines Development Process

Basis for Recommendations

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

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

(1) it is expected that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation of adult efficacy data to pediatric patients;

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

(3) studies supporting the safety of the drug in pediatric patients are provided[12].

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

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

- **Quality of Evidence Rating I–Randomized Clinical Trial Data.**
  In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.
  - Quality of Evidence Rating I will be used if there are data from large randomized trials in children with clinical and/or validated laboratory endpoints.
  - Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. For example, if a randomized Phase III clinical trial in adults demonstrates a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population, a rating of I* may be used for quality of evidence.
- **Quality of Evidence Rating II–Nonrandomized Clinical Trials or Observational Cohort Data.** In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data may be used if there are sufficient pediatric data consistent with high-quality adult studies.
  - Quality of Evidence Rating II will be used if there are data from well-designed nonrandomized trials or observational cohorts in children.
  - Quality of Evidence Rating II* will be used if there are well-designed nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. For example, if a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 cell count and observational data in children indicate that a similar CD4 count is associated with clinical outcomes in children older than a specific age, a rating of II* may be used for quality of evidence.
- **Quality of Evidence Rating III–Expert opinion.**
  The criteria do not differ for adults and children.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B: Moderate recommendation for the statement** **C: Optional recommendation for the statement**	**I:** One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion
†Studies that include children or children/adolescents but not studies limited to postpubertal adolescents	

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

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

- Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States[13]. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*
- The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all ARV drugs produced.
- Although some information regarding the efficacy of ARV drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of Phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved ARV drug in children.
- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a

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

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

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

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Identification of Perinatal HIV Exposure (Updated August 11, 2011)

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 is recommended for women who have negative HIV antibody tests earlier in pregnancy if they are at high risk of HIV infection because of behavior or residence in a high-prevalence area **(AII)**. • Women seen at labor with undocumented HIV status should undergo rapid HIV antibody testing, and women with a positive antibody test should initiate intrapartum antiretroviral (ARV) prophylaxis **(AII)**. • If acute HIV infection is suspected in a pregnant woman, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection **(AII)**. • Women who have not been tested for HIV 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 the mother or infant is HIV antibody positive, infant ARV prophylaxis should be initiated as soon as possible and the mother advised not to breastfeed pending results of confirmatory HIV antibody testing **(AII)**.

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

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

- HIV-infected women to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections (OIs) for their own health;
- Provision of 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 advising against breastfeeding 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 4-6 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 in the third trimester, preferably before 36 weeks gestation, is recommended for women with initially negative HIV antibody tests who are at high risk of HIV infection and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criterion:

- receive health care in jurisdictions with a high incidence of HIV or AIDS among women 15–45 years of age;
- receive 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 (e.g., injection drug users or partners of injection drug users, exchange sex for money or drugs, are sex partners of HIV-infected persons, and have had a new or more than 1 sex partner during current pregnancy or diagnosis of a new sexually transmitted infection [STI] during pregnancy); and
- have signs or symptoms of acute HIV infection[3, 6, 16].

Women who declined testing earlier in pregnancy should have testing offered again during the third trimester. There is evidence that the risk of HIV acquisition is significantly higher during pregnancy than in the postpartum period[17]. If acute HIV infection is suspected, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection.

Rapid HIV Testing During Labor in Women with Unknown HIV Status

Use of rapid test kits or an expedited enzyme-linked immunosorbant assay (ELISA) to detect HIV antibodies is recommended to screen women who are seen at labor and have undocumented HIV status in order to identify HIV exposure in their infants[2-3, 6, 15]. Any hospital offering intrapartum care should have rapid HIV testing available and should have in place policies and procedures to assure that staff are prepared to provide patient education about rapid HIV testing, that appropriate ARV medications are available whenever needed, and that follow-up procedures for women found to be HIV infected and their infants are in place. Rapid tests have been found to be feasible, accurate, timely, and useful both in assuring prompt initiation of intrapartum and neonatal ARV prophylaxis and in reducing perinatal transmission of HIV[18]. Results of rapid tests can be obtained within minutes to a few hours and are as accurate as standard ELISA antibody testing[19-20]. 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[20]. A single negative rapid test does not need confirmation unless acute HIV infection is suspected, in which case a virologic test is necessary. The 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, 5, 8, 15].

HIV Counseling and Testing During 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 counseling and consent of the mother unless state law allows testing without consent[2-3, 8, 15]. Because neonatal ARV chemoprophylaxis should be initiated as soon as possible after birth, and no later than 12 hours after birth, to be effective in preventing mother-to-child transmission (MTCT)[21-22], use of rapid

HIV antibody assays or expedited ELISA testing to allow prompt identification of HIV-exposed infants is essential. It is strongly recommended that infant ARV prophylaxis be initiated while awaiting confirmatory testing results after an initial positive rapid test in the mother or the infant and that women with positive rapid HIV test results be advised not to initiate breastfeeding pending results of confirmatory testing. If the confirmatory test is negative, the infant ARV prophylaxis can be discontinued and the mother can initiate breastfeeding. Mechanisms should be developed to facilitate rapid HIV screening for infants who have been abandoned and are in the custody of the state.

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Diagnosis of HIV Infection in Infants (Updated August 11, 2011)

Panel's Recommendations:
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months **(AII)**. HIV antibody testing cannot establish HIV infection in this age group because maternal HIV antibodies may persist and interfere with the interpretation of a positive HIV antibody test.
• Virologic diagnostic testing is recommended in infants with known perinatal HIV exposure at ages 14–21 days, 1–2 months, and 4–6 months **(AII)**.
• Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection **(BIII)**.
• HIV DNA polymerase chain reaction (PCR) and HIV RNA assays are recommended as preferred virologic assays **(AII)**.
• Confirmation of HIV infection should be based on two positive virologic tests obtained from separate blood samples **(AI)**.
• Definitive exclusion of HIV infection (in the absence of breastfeeding) should be based on at least two negative virologic tests (one at >1 month and one at ≥4 months of age) **(AII)**.
• Some experts confirm the absence of HIV infection at 12–18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
• In children ≥18 months of age, HIV antibody assays alone can be used for diagnosis **(AII)**.

Choice of Diagnostic Test

HIV infection can be definitively diagnosed through the use of virologic assays in most nonbreastfed HIV-infected infants by 1 month of age and in virtually all infected infants by 4 months of age. Tests for antibodies to HIV, including newer rapid tests, do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies; therefore a virologic test should be used[1]. A positive virologic test (i.e., detection of HIV by DNA 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. The use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in the first months of life are less than that of other HIV virologic tests[2-3].

HIV DNA PCR

HIV DNA PCR is a sensitive technique used to detect specific HIV viral DNA in peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at <48 hours of age is less than 40% but increases to more than 90% by 2–4 weeks of age[4-5].

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in the plasma and are as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. Studies have demonstrated sensitivities of 25%–40% during the first weeks of life, increasing to 90%–100% by 2–3 months of age[4-8]. Similarly, specificity is comparable between the two tests, although the detection of low levels of HIV RNA (<5,000 copies/mL) may not be reproducible and tests with low levels of HIV RNA should be re-

peated before they are interpreted as documenting HIV infection in an infant. An HIV RNA assay can be used as the confirmatory test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (see HIV subtype section below). It is established that HIV DNA PCR remains positive even in individuals receiving therapeutic highly active antiretroviral therapy (HAART)[9]. However, whether the sensitivity of RNA assays might be affected by maternal antenatal therapy with combination antiretroviral (ARV) drugs and/or infant ARV prophylaxis is unknown.

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing[10-13].

HIV Culture

HIV culture is not used for routine HIV diagnostic testing. It is generally not available outside of research laboratories. Although HIV culture has a sensitivity similar to that of HIV DNA PCR[14], it is more complex and expensive to perform than DNA PCR or RNA assays and may require 2–4 weeks for definitive results.

Issues Related to Diagnosis of Non-Subtype B HIV Infection

Although HIV subtype B is the predominant viral subtype found in the United States, non-subtype B viruses predominate in some other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia[15-17]. 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[18-21]. 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[22].

Some of the currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection[23-26], although even these assays may not detect or properly quantify some non-B subtypes, particularly the more uncommon group O HIV subtypes[25, 27-28]. When non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR, repeat testing using one of the newer RNA assays shown to be more sensitive in the detection of non-subtype B HIV (e.g., Amplicor HIV-1 Monitor 1.5 [Roche Molecular Systems, Pleasanton, CA], NucliSens HIV-1 QT [bioMerieux, Inc., Durham, NC], Versant Quantiplex HIV RNA 3.0 [branched DNA/bDNA] [Bayer Corporation, Tarrytown, NY], AmpliPrep/TaqMan HIV-1 Test [Roche Diagnostics, Indianapolis, IN], Real Time HIV-1 Assay [Abbott Molecular Incorporated, Des Plaines, IL], and the APTIMA HIV-1 RNA Qualitative Assay [Gen-Probe Incorporated San Diego, CA]) is recommended.

When evaluating an infant whose mother and/or father comes from an area endemic for non-subtype B HIV, such as Africa and Southeast Asia, clinicians should consider conducting initial testing using one of the assays more sensitive for non-subtype B virus (for example, one of the newer RNA assays mentioned above)[25, 29]. When non-subtype B infection is suspected in a child with negative HIV DNA PCR and RNA assays, the clinician should consult with an expert in pediatric HIV infection. The child should undergo close clinical monitoring and definitive HIV serologic testing at age 18 months.

Timing of Diagnostic Testing in Infants with Known Perinatal HIV Exposure

Virologic diagnostic testing of the HIV-exposed infant should be performed at ages 14–21 days, 1–2

months, and 4–6 months. Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection (see below).

Two positive virologic tests obtained from separate blood samples provide confirmation of HIV infection on regardless of child's age. A positive HIV antibody test with confirmatory Western blot (or immunofluorescent antibody [IFA] assay) at age ≥18 months confirms HIV infection with the exception of rare late seroreverters (see HIV antibody section below)[1].

HIV infection can be *presumptively* excluded in nonbreastfed infants with two or more negative virologic tests, with one test obtained at ≥14 days of age and one obtained at ≥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, 30]. *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at 4–6 weeks of age until they are determined to be HIV uninfected or *presumptively* uninfected with HIV[31]. Thus, initiation of PCP prophylaxis can be avoided or, if prophylaxis was initiated, can be stopped, if the infant has negative virologic tests at 2 weeks of age and at ≥4 weeks of age, or if virologic testing is negative at ≥8 weeks of age.

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

Virologic Testing at Birth (Optional)

Virologic testing at birth may be considered for newborns at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal ART or who had HIV viral loads >1,000 copies/mL close to the time of delivery. As many as 30%–40% of HIV-infected infants can be identified by 48 hours of age[4]. Blood samples from the umbilical cord should not be used for diagnostic evaluations due to the potential contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection during the intrauterine period from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection[32]. 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[32-33]. 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[34]. 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[34].

Virologic Testing at Age 14–21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks[4], 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 1–2 Months

Infants with negative virologic tests before 1 month of age should be retested at 1−2 months of age. Most HIV-exposed neonates will receive 6 weeks of neonatal ARV prophylaxis. Although ARV agents could theoretically affect the predictive value of HIV virologic testing in neonates, the use of prenatal/intrapartum/neonatal zidovudine single-drug prophylaxis did not delay the detection of HIV by culture in infants in PACTG protocol 076 and has not decreased the sensitivity and predictive values of many virologic assays[6-8, 30, 35-36]. The effect of prenatal and neonatal combination ARV regimens on the sensitivity of virologic tests for HIV-exposed infants needs to be examined. An infant with two negative virologic tests, one at ≥14 days and one at ≥1 month of age, can be viewed as *presumptively* uninfected and would not need PCP prophylaxis, assuming the child has no laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection.

Virologic Testing at Age 4–6 Months

HIV-exposed children who have had repeatedly negative virologic assays at 14–21 days of age and at 1–2 months of age, have no clinical evidence of HIV infection, and are not breastfed should be retested at 4–6 months of age for *definitive* exclusion of HIV infection.

Antibody Testing at Age 6 Months or Older

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

Antibody Testing at Age 12–18 Months to Document Seroreversion

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 to the infant *in utero* have disappeared.The proportion of infants who serorevert by 15–18 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 the staging of maternal disease and the sensitivity of the assay[1, 37-40].

Antibody Testing at Age 18 Months or Older

HIV infection can be diagnosed in children 18 months of age or older with a positive HIV antibody test and a confirmatory Western blot (or IFA assay).

On rare occasions, nonbreastfed HIV-exposed infants with no other route of HIV transmission (e.g., receipt of contaminated blood products, sexual abuse by HIV-infected person, or receipt of solid food premasticated by an HIV-infected caregiver) and no clinical or virologic laboratory evidence of HIV infection may have residual antibodies at 18 months of age. These infants should have repeat antibody testing because they may be late seroreverters, which can occur as late as 24 months of age[40]. In such cases, some experts would repeat virologic testing if the confirmatory HIV antibody test is positive at 18 months of age. This is due to reports, although rare, of late postnatal diagnoses despite negative virologic tests through 6 months of age as well as false-negative HIV DNA PCR assays in infants infected with non-subtype B HIV[18-21, 41].

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Laboratory Monitoring of Pediatric HIV Infection Before Initiation of Therapy (Updated August 11, 2011)

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

Immunologic Monitoring in Children

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

In HIV-infected children, as in infected adults, the CD4 count and percentage decline as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values (Tables 3–5). Consequently, CD4 values should be obtained as soon as possible after a child has a positive test for HIV and every 3 to 4 months thereafter. 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 young infants with HIV infection may have rapid disease progression[6-7], some experts monitor CD4 percentage more frequently (e.g., every 1-2 months) in untreated infants younger than 6-12 months of age. 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 (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 (the HIV Paediatric Prognostic Markers Collaborative Study [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 death based on the child's age and selected values of CD4 percentage and HIV RNA copy number at baseline. Figures 1 and 2 and Table 3 depict age-associated 1-year risk of developing AIDS or death as a function of CD4 percentage. In a separate analysis of this data set, predictive value of absolute CD4 cell count for risk of death or AIDS/death in HIV-infected

children 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, 8].

The risk of disease progression associated with a specific CD4 percentage or count varies with the age of the child. Infants in the first year of life experience higher risks of progression or death than older children for any given CD4 stratum. For example, comparing a 1-year-old child with 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 age 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 age 5 years of age or older with CD4 counts greater than 350 cells/mm^3, although in younger children there continued to be a significant risk of death even with CD4 cell counts greater than 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 Web site 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 or HIV-1 RNA viral load measurement (http://hppmcs.org)[4].

Measurement of CD4 values can be associated with considerable intrapatient variation[5]. Even mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in CD4 count and percentage; thus, CD4 values are best measured when patients are clinically stable. No decision about therapy

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 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)*

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

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

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 following acute infection[9-10]. In infected adults, the viral set point correlates with the subsequent risk of disease progression or death[11-12].

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[13-14]. 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[15]. In addition, in contrast to the adult pattern, after the first year of life, HIV

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*

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

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

† Mean follow-up: 5.1 years.

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

¶ Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. J Infect Dis. 1997;175(5):1029–1038.

Figure 1. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[Modified from Lancet 2003;362:1605-1611]*

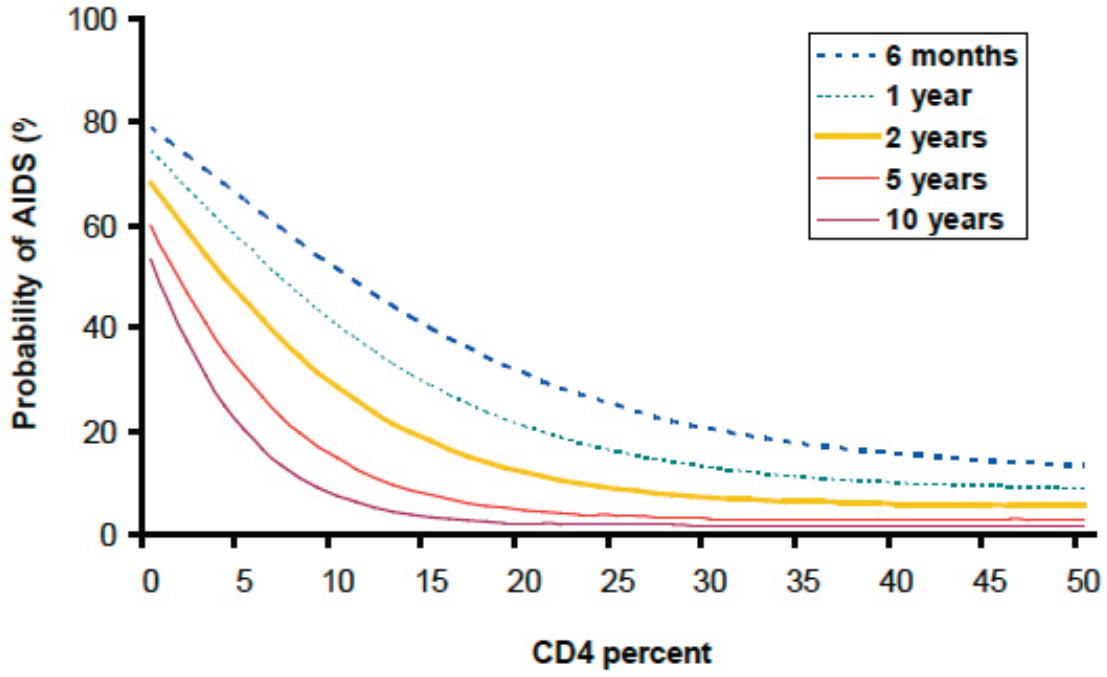


Figure 2. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[Modified from Lancet 2003;362:1605-1611]*

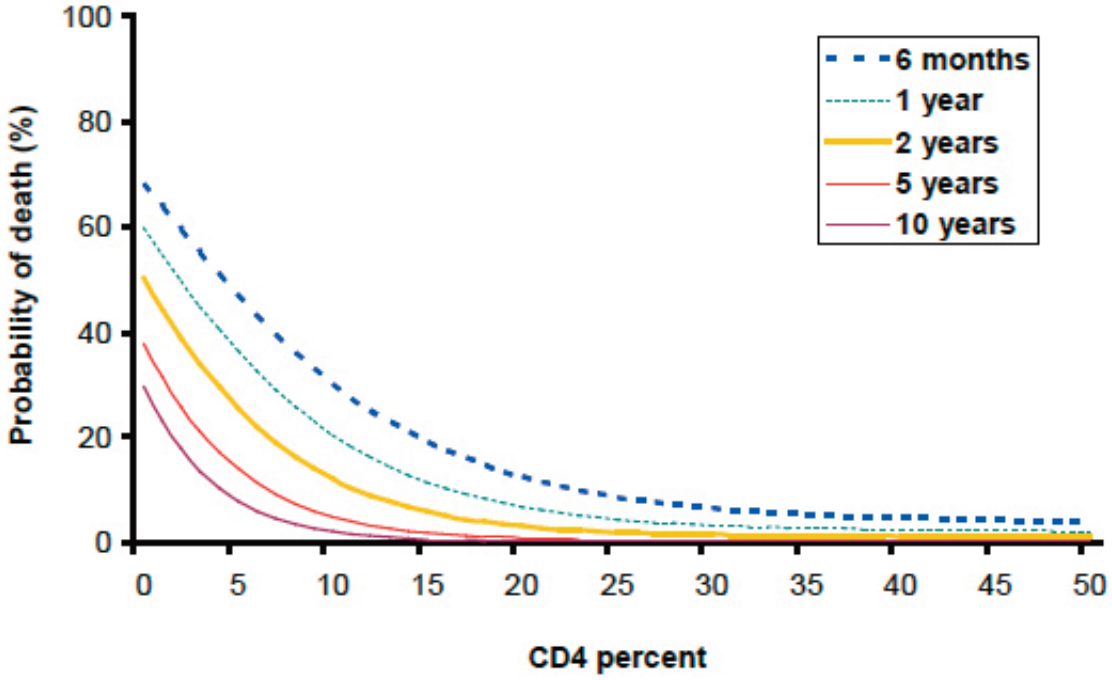


Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults in the CASCADE Study *[Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. J Infect Dis. 2008;197:398-404.]*

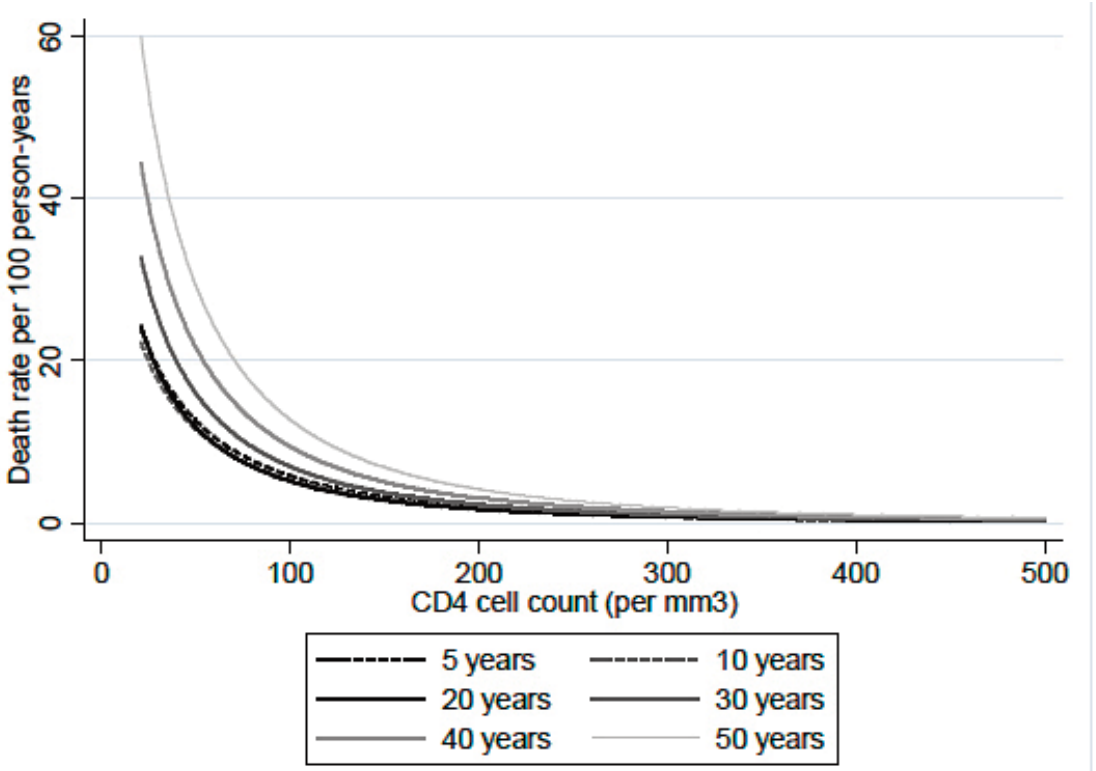


Figure 4. Estimated Probability of AIDS Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[Modifed from Lancet 2003;362:1605-1611.]*

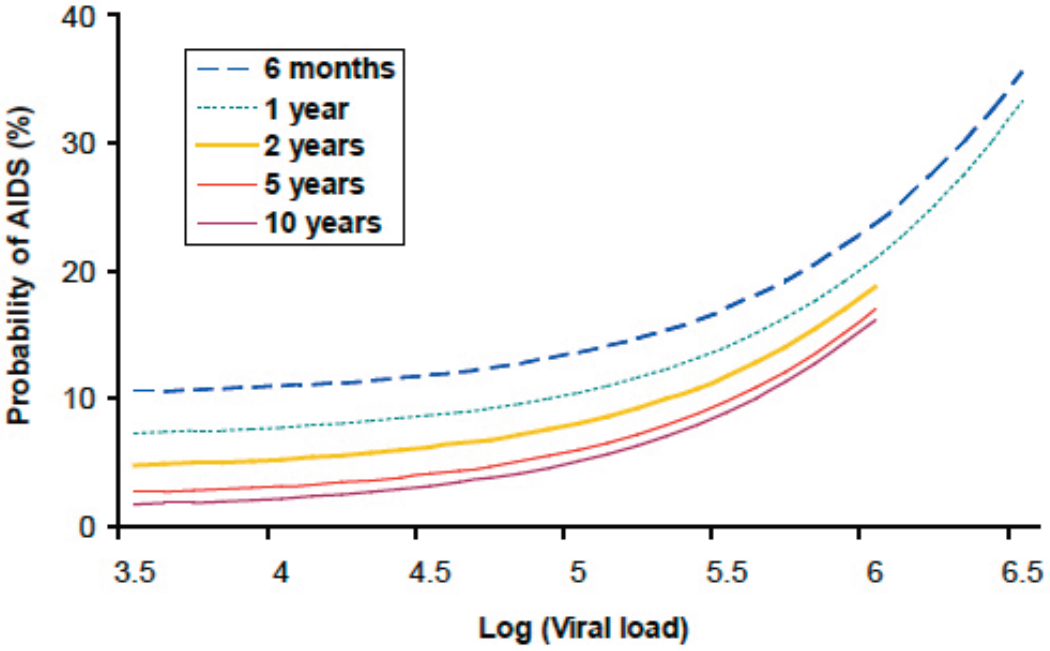
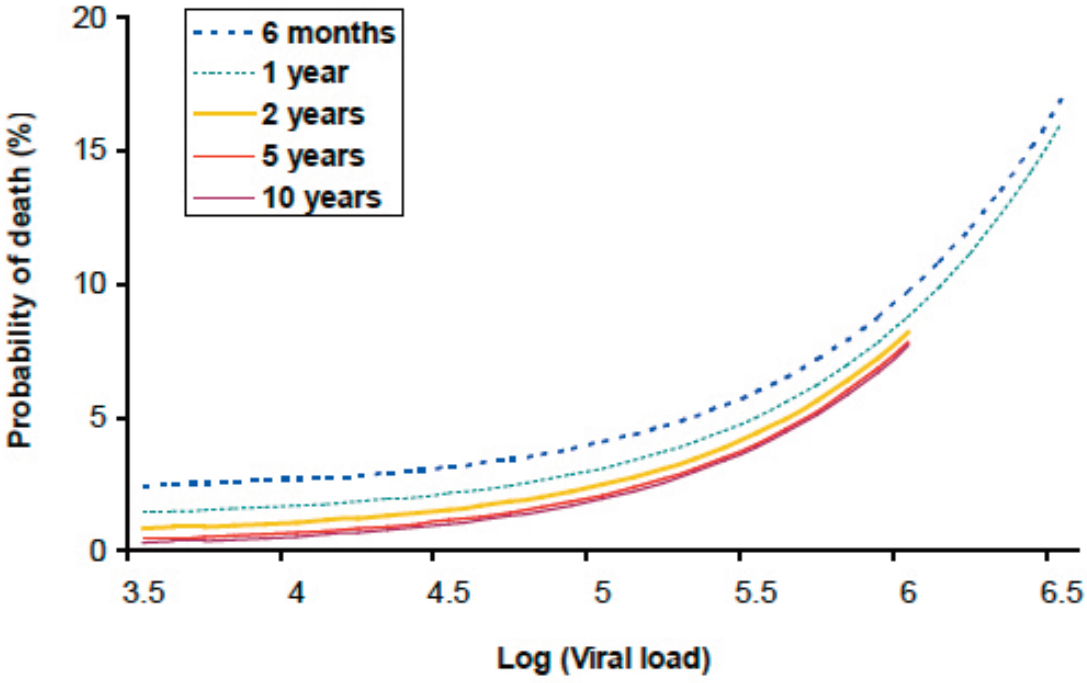


Figure 5. Estimated Probability of Death Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[Modifed from Lancet 2003;362:1605-1611.]*



RNA copy number slowly declines over the next few years[15-18]. 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[19].

High 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[13-15]. High RNA levels (i.e., levels of >100,000 copies/mL) in older children have also been associated with high risk of disease progression and mortality, particularly if CD4 percentage is less than 15% (Table 5)[17-18]. 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[17-18], 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[17]. 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[14]. 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[17-18, 20-22].

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 Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

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[25-28].

Five Food and Drug Administration (FDA)-approved viral load assays using one of three 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 detection differs between the "ultrasensitive" assay (<50 copies/mL) and the "regular sensitivity" assay (<400 copies/mL); the AmpliPrep/TaqMan HIV-1 Test (Roche Diagnostics); and the Real Time HIV-1 Assay (Abbott Molecular Incorporated);
- HIV-1 nucleic acid sequence-based amplification test (NucliSens HIV-1 QT, bioMerieux); and

- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (VERSANT HIV-1 RNA 3.0 Assay, Bayer).

The lower limits of detection of the assays differ (<40 copies/mL for the Abbott Real Time HIV-1 test, <48 copies/mL for the AmpliPrep/TaqMan HIV-1 Test, <50 copies/mL for the Amplicor HIV-1 Monitor Test, <80 copies/mL for the NucliSens HIV-1 QT assay, and <75 copies/mL for the VERSANT assay). Use of ultrasensitive viral load assays 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.

The predominant virus subtype in the United States is B, which is the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes, with the exception of the uncommon O subtypes[29-30]. This is important for many regions of the world where non-B subtypes are predominant as well as for the United States, where a small subset of individuals are infected with non-B viral subtypes[31-33]. 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 amount of blood (100 µL of plasma), followed by the RT-PCR assays such as Amplicor HIV-1 Monitor (200 µL of plasma) and the VERSANT assays (1 mL of plasma).

Biologic variation in HIV RNA levels within one person is well documented. In adults, repeated measurement of HIV RNA levels using the same assay can vary by as much as threefold (0.5 $\log_{10}$ copies/mL) in either direction over the course of a day or on different days[20, 24, 27]. This biologic variation may be greater in infected infants and young children. In children with perinatally acquired HIV infection, RNA copy number slowly declines even without therapy during the first several years after birth, although it persists at higher levels than those observed in most infected adults[15-17]. This decline is most rapid during the first 12-24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ copies/mL per year; a slower decline continues until approximately 4-5 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 ages 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.

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Treatment Recommendations (Updated August 11, 2011)

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 (OIs) 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[6-7]; 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[8-10] (see Management of Medication Toxicity or Intolerance and Table 17).

ARV drug-resistant virus can develop in both multidrug-experienced children and children who received initial regimens containing one or two drugs that incompletely suppressed viral replication. Additionally, primary drug resistance may be seen in ARV-naive children who have become infected with a resistant virus[11-12]. 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.

A number of factors need to be considered in making decisions about initiating and changing antiretroviral therapy (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)[13-14], level of CD4 cell immunosuppression, and magnitude of HIV plasma viremia;
- availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in the child's age group;
- potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the ARV regimen;
- effect of initial regimen choice on later therapeutic options;
- the child's ARV treatment history;
- presence of ARV drug-resistant virus;
- presence of comorbidity, such as tuberculosis (TB), hepatitis B virus (HBV) or hepatitis C virus (HCV) 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 the child; and
- the ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most 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. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

Goals of Antiretroviral Treatment

Current ARVs do not eradicate HIV infection because of the long half-life of latently infected CD4 cells[15-17]; 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)[18]. 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 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; and
- improving quality of life.

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

Use and selection of combination antiretroviral therary (cART): At present, 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 unless required (e.g., severe toxicity or intolerance or significant clinical, immunologic, or virologic progression). Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Currently, recommendations for initial therapy are to use two classes of drugs–two nucleoside reverse

transcriptase inhibitors (NRTIs) combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI)—thereby sparing three classes of drugs for later use.

Maximizing adherence: As discussed in Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents, poor adherence to prescribed regimens can lead to subtherapeutic levels of ARV medications, which enhances the risk of the development of drug resistance and likelihood of virologic failure. Participation by the caregiver and child in the decision-making process is crucial. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with the child's caregiver and the child (when age appropriate) before the decision to initiate therapy is made. Potential problems should be identified and resolved before starting therapy, even if this delays initiation of therapy. Additionally, 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 Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories*

Category N: Not Symptomatic
Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.
Category A: Mildly Symptomatic
Children with **two** or more of the following conditions but none of the conditions listed in Categories B and C: • Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory infection, sinusitis, or otitis media
Category B: Moderately Symptomatic
Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following: • Anemia (<8 gm/dL), neutropenia (<1,000 cells/mm^3), or thrombocytopenia (<100,000 cells/mm^3) persisting ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children age >6 months • Cardiomyopathy • Cytomegalovirus infection with onset before age 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month • Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Fever lasting >1 month • Toxoplasmosis with onset before age 1 month • Varicella, disseminated (i.e., complicated chickenpox)

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

Category C: Severely Symptomatic
Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (below), with the exception of LIP (which is a Category B condition): • Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections) • Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs) • Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes) • Cryptococcosis, extrapulmonary • Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month • Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes) • Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance • Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age • Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes) • Kaposi's sarcoma • Lymphoma, primary, in brain • Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype • Mycobacterium tuberculosis, disseminated or extrapulmonary • Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes) • *Mycobacterium avium* complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes) • *Pneumocystis jiroveci* pneumonia • Progressive multifocal leukoencephalopathy • Salmonella (nontyphoid) septicemia, recurrent • Toxoplasmosis of the brain with onset at >1 month of age • Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **PLUS** 1) chronic diarrhea (i.e., ≥ two loose stools per day for >30 days), **OR** 2) documented fever (for ≥30 days, intermittent or constant)

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

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When to Initiate Therapy in Antiretroviral-Naive Children (Updated August 11, 2011)

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 controls viral replication before the onset of rapid genetic mutation and evolution into multiple quasispecies, resulting in a lower viral set point, fewer mutant viral strains, and potentially less drug resistance[1]. Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression. Additionally, 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]. 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 because of 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 toxicities are particularly important.

Randomized clinical trials have demonstrated the benefit in reducing mortality and morbidity with initiation of therapy in infants <12 weeks of age with normal CD4 percentage[9] and in adults with CD4 cell counts <350 cells/mm^3 [10]. However, clinical trial data on the optimal time to start treatment in older children or in adults with higher CD4 cell counts are lacking.

Based on observational cohort data demonstrating benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm^3 in reducing morbidity and mortality, adult treatment guidelines recommend initiation of lifelong ART for individuals with CD4 cell counts ≤500 cells/mm^3 [11–14]. For adults with CD4 counts >500 cell/mm^3, observational data are inconclusive regarding the potential survival benefit of early treatment. Adult treatment guidelines note that some experts would recommend initiation of therapy at this CD4 level, while other experts would view initiation at this level as optional[13].

Recommendations on when to initiate therapy have generally been more aggressive in young children than in adults. HIV infection in children is primarily perinatally acquired, which makes it possible to identify the time of infection. HIV disease progression is more rapid in young children than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for infants younger than 1–2 years of age. As discussed in Laboratory Monitoring of Pediatric HIV Infection, CD4 counts and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children <12 months of age[15]. Hence, recommendations for when to start therapy differ by age of the child. Based on data showing that surrogate marker-based risk of disease progression to AIDS or death varies considerably by age but that CD4 count-associated risk of progression in children ≥5 years of age is similar to risk in young adults[16], the Panel has moved to recommendations for initiation of treatment for three age bands: infants <12 months of age, children 1 to <5 years of age, and children and adolescents ≥5 years of age.

Antiretroviral-Naive HIV-Infected Infants 12 Months or Younger

Panel's Recommendations (Table 7)
• Antiretroviral therapy (ART) should be initiated in HIV-infected infants <12 months of age, regardless of clinical status, CD4 percentage, or viral load **(AII)**..
• Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated **(AIII)**.

Data from the South African CHER Trial (Children with HIV Early Antiretroviral Therapy) demonstrated that initiating triple-drug ART before 12 weeks of age in asymptomatic perinatally infected children with normal CD4 percentage (CD4 percentage >25%), compared with delaying treatment until the child met clinical or immune criteria, resulted in a 75% reduction in early mortality[9]. Most of the deaths in the children 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 from the CHER study, the Panel recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage, or viral load (Table 7). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with the 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 the child, with the youngest children at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in infected infants; by 12 months of age, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression[17]. 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[18]. 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 counts[18].

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[6,19-21]. Several small studies have demonstrated that despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. However, therapy is not curative; proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued[22-23].

However, virologic suppression may take longer in young children (given their higher viral load at initiation of therapy) than in older children or adults[24-25]. Possible reasons for the poor response in infants include very high viral loads in young infants, inadequate antiretroviral (ARV) drug levels, and poor

adherence due to the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70%–80% have been reported in HIV-infected infants initiating therapy at <12 months of age[6,26-27]. In a 5-year follow-up study of 40 HIV-infected children who

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

Table 7 provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with the child (if age appropriate) and the caregiver.

Age Bands	Criteria for Therapy Initiation	Recommendations
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat* ***(AII)***
1 to <5 years	• AIDS or significant HIV-related symptoms[a]	*Treat* ***(AI*)***
	• CD4 percentage <25%, regardless of symptoms or HIV RNA level	*Treat* ***(AII)***
	• Asymptomatic or mild symptoms[b] *and*	*Treat* ***(BII)***
	o CD4 percentage ≥25% *and*	
	o HIV RNA ≥100,000 copies/mL	
	• Asymptomatic or mild symptoms[b] *and*	*Consider Treatment*[c] ***(CIII)***
	o CD4 percentage ≥25% and	
	o HIV RNA <100,000 copies/mL	
≥5 years	• AIDS or significant HIV-related symptoms[a]	*Treat* ***(AI*)***
	• CD4 count ≤500 cells/mm^3	*Treat* *CD4 count <350 cells/mm^3* ***(AI*)*** *CD4 count 350–500 cells/mm^3* ***(BII*)***
	• Asymptomatic or mild symptoms[b] *and*	
	o CD4 count >500 cells/mm^3 *and*	*Treat* ***(BII*)***
	o HIV RNA ≥100,000 copies/mL	
	• Asymptomatic or mild symptoms[b] *and*	*Consider Treatment*[c] ***(CIII)***
	o CD4 count >500 cells/mm^3 *and*	
	o HIV RNA <100,000 copies/mL	

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

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

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

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[6].

Information on appropriate drug dosing in infants younger than 3–6 months is limited. Hepatic and renal functions are immature in the newborn undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children. 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 in the treatment of young infants (see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents).

Finally, the possibility of toxicities—such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction—with prolonged therapy is a concern[28]. Whether it might be possible to stop therapy begun in early infancy after a defined period of treatment (e.g., 1–2 years) that protected the child during the period of greatest risk of HIV disease progression and mortality, and then restart therapy when the child meets standard age-related criteria, is under assessment in a clinical trial in South Africa.

Antiretroviral-Naive HIV-Infected Children 1 Year or Older

Panel's Recommendations (Table 7)

• Antiretroviral therapy (ART) should be initiated in children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level **(AI*)**.
• Initiation of ART is also recommended for children age ≥1 year regardless of symptoms or plasma HIV RNA level if:
  • age 1 to <5 years and CD4 percentage <25% **(AII)**; or
  • age ≥5 years and CD4 count ≤500 cells/mm^3 (**AI*** for CD4 percentage <25% or CD4 count <350 cells/mm^3 and **BII*** for CD4 count 350–500 cells/mm^3).
• Initiation of ART is also recommended for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or a single episode of serious bacterial infection) with a plasma RNA ≥100,000 copies/mL regardless of CD4 percentage/count **(BII*)**.
• Initiation of ART may be considered for children age ≥1 year who are asymptomatic or have mild symptoms with a plasma RNA RNA <100,000 copies/mL and CD4 percentage >25% if age 1–5 years or CD4 count >500 cells/mm^3 if age ≥5 years **(CIII)**.

Disease progression is less rapid in children age ≥1 year[17]. Children with clinical AIDS or significant symptoms (Clinical Category C or B—Table 6)[29] 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 age ≥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[30]. 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 count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, considerations related to initiation of ART in asymptomatic individuals are based primarily on risk of disease progression as determined by baseline CD4 count[13]. In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 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 counts fell to <350 cells/mm^3 compared with deferring treatment until CD4 counts fell to <200 cells/mm^3 [9]. 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 showed the risk of AIDS or death was significantly less in adults who started treatment with CD4 counts of 200–350 cells/mm^3 compared with those who started therapy at CD4 counts of <200 cells/mm^3 [31].

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 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 counts of 351–500 cells/mm^3 [11–12]. The NA-Accord study demonstrated a benefit of starting treatment at CD4 counts >500 cells/mm^3 compared with starting ART at CD4 counts below this threshold[11]; however the ART-CC cohort found no additional benefit for patients starting ART with CD4 counts >450 cells/mm^3 [11]. There are no similar observational data analyses for HIV-infected children. The Health and Human Services (HHS) Adult Antiretroviral Guidelines Panel recommends initiation of therapy for adults with CD4 cell counts ≤500 cells/mm^3. The Adult Panel, however, was divided on recommendations regarding starting therapy in HIV-infected adults with CD4 counts >500 cells/mm^3. Some experts recommend initiation of treatment while others feel that, at this level, therapy should be optional and considered on a case-by-case basis[32].

In children, the prognostic significance of a specific CD4 percentage or count varies with age[15,18]. 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 among children age 1–4 years than among children age ≥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) [16,18]. For children age 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (Table 3).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count[15]. Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[33-35]; similar findings have been reported in adults[36]. 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 age >1 year when HIV RNA levels were ≥100,000 copies/mL (Table 3 and Figures 4–5)[15]. For example, the estimated 1-year risk of death was 2−3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8−10 times higher with plasma HIV RNA >1,000,000 copies/mL.

Similar to data in adults, data from pediatric studies suggest the immune response to treatment in children is better when treatment is initiated at higher CD4 percentage/count levels[25,37]. 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%–24% achieved CD4 percentage >25% after 5

years of therapy[38]. Younger age at initiation of therapy has also been associated with improved immune response and with more rapid growth reconstitution[37-39]. Given that disease progression in children age ≥5 years is similar to that in adults[15], and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is ≤500 cells/mm^3 [11–12], some 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.

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 no ART[40-42].

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

For children age ≥5 years, ART should be initiated if they 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. Additionally, treatment is recommended for children in this age group if they have CD4 counts ≤500 cells/mm^3, regardless of clinical symptoms or HIV RNA level. The evidence for this recommendation is strongest for children with CD4 counts <350 cells/mm^3. For children with CD4 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 is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection [Table 6]) with CD4 counts >500 cells/mm^3 if HIV RNA is >100,000 copies/mL. ART may be considered for asymptomatic or mildly symptomatic children age ≥5 years who have CD4 counts >500 cells/mm^3 and who also have plasma HIV RNA levels <100,000 copies/mL.

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 age ≥5 years given their lower risk of disease progression and the higher CD4 count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor the 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 (e.g., HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for consideration of therapy;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

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What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children (Updated August 11, 2011)

Panel's Recommendations
• Combination therapy, including either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, 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 of ultrasensitive assays and to preserve or normalize immune status **(AI)**.
• Antiretroviral (ARV) drugs initiated for chemoprophylaxis of mother-to-child (MTCT) transmission of HIV should be discontinued in infants who are identified as HIV infected **(AI)**.
• ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive children (**AII** infants; **AIII** children).

General Considerations

More than 20 ARV drugs are approved for use in HIV-infected adults and adolescents; 17 have an approved pediatric treatment indication and 15 are available as a pediatric formulation or in a capsule size suitable for pediatric use. ARV drugs fall into several major drug classes: NRTIs, NNRTIs, PIs, 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[3-6]. The goal of antiretroviral therapy (ART) is to maximally suppress viral replication, preferably to undetectable levels, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used[5-7].

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

Treatment-naive children with perinatal HIV infection can have drug-resistant virus, either by acquisition of a resistant virus from their mother or by developing resistance while receiving ARV prophylaxis. Thus, ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive children. In infants receiving prophylactic ARV drugs for prevention of perinatal transmission of HIV, ARV drug-resistance testing can be performed at the same time as confirmatory HIV testing or when

prophylactic ARV drugs are discontinued. Drug-resistant virus has been identified in 6%–16% of ARV-naive adults and 18% of behaviorally infected adolescents with recent infection in the United States and Europe[8-12]. Data from children in resource-rich regions are limited. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and in 19% of 42 infants born from 2000 to 2001[13-14]. 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[15]. Thus, the prevalence of infants infected with ARV drug-resistant virus may be increasing and may not necessarily be predicted by the drug prophylaxis regimen received by the mother. In a study in Africa, infants, regardless of whether they were exposed to single-dose nevirapine as part of prophylaxis to prevent HIV MTCT, had higher rates of virologic failure on nevirapine-based regimens compared with lopinavir/ritonavir-based regimens[1-2]. 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[16]. Nevertheless, because the prevalence of resistance in HIV-infected children is sufficiently high and based on expert opinion, the Panel recommends resistance testing before initiation of therapy in all treatment-naive children and use of resistance testing results to select the initial combination therapy[17]. Recommendations on resistance testing in HIV-infected adults are similar.

Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Table 8)

Panel's Recommendations

- The Panel recommends initiating antiretroviral therapy (ART) in treatment-naive children using one of the following agents (in alphabetical order) plus a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone combination:
  - For children ≥42 weeks of postmenstrual age and postnatal ≥14 days of age: lopinavir/ritonavir **(AI)**
  - For children age ≥3 years: efavirenz **(AI*)**
  - For children age ≥6 years: atazanavir/ritonavir **(AI*)**.
- The Panel recommends the following preferred dual-NRTI backbone combinations:
  - 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*)**.
  - Zidovudine + (lamivudine or emtricitabine) **(AI*)**
  - For adolescents ≥12 years of age and Tanner Stage 4 or 5: tenofovir + (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 preferred for some patients based on their individual characteristics and needs.

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children
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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 11–13).

Preferred Regimens	
Children age ≥14 days and <3 years[1]	Two NRTIs ***plus*** LPV/r
Children age ≥3 years	Two NRTIs ***plus*** EFV[2] Two NRTIs ***plus*** LPV/r
Children age ≥6 years	Two NRTIs ***plus*** ATV plus low-dose RTV Two NRTIs ***plus*** EFV[2] Two NRTIs ***plus*** LPV/r
Alternative Regimens	
Children of any age	Two NRTIs ***plus*** NVP[3]
Children age ≥6 years	Two NRTIs ***plus*** DRV plus low-dose RTV Two NRTIs ***plus*** FPV plus low-dose RTV
Regimens for Use in Special Circumstances	
Two NRTIs ***plus*** ATV unboosted (for treatment-naive adolescents age ≥13 years and body weight >39 kg) Two NRTIs ***plus*** FPV unboosted (children age ≥2 years) Two NRTIs ***plus*** NFV (children age ≥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 age ≥3 months) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 4 or 5 only) ZDV ***plus*** (3TC ***or*** FTC)
Alternative	ddI ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 3) ZDV ***plus*** ABC ZDV ***plus*** ddI
Use in Special Circumstances	d4T ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 2)

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children
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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 11–13).

Not Recommended or Insufficient Data to Recommend for Initial Therapy	
	ETR-containing regimens EFV-containing regimens for children age <3 years TPV-containing regimens SQV-containing regimens 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 age <13 years and/or body weight <39 kg NFV-containing regimens for children age <2 years Unboosted DRV-containing regimens Once-daily dosing of LPV/r, boosted DRV, or boosted or unboosted FPV Triple-NRTI regimens other than ABC + ZDV + 3TC Triple-class regimens, including NRTI plus NNRTI plus PI Regimens with dual-NRTI backbones of ABC + ddI, ABC + TDF, ddI + TDF, and ddI + d4T TDF-containing regimens in children age <12 years or children age ≥12 years and Tanner Stage 1 MVC-containing regimens Rilpivirine-containing regimens RAL-containing regimens T-20-containing regimens

[1] 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.

[2] EFV is currently available only in capsule form and should be used only in children age ≥3 years who weigh ≥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.

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; 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; TMC-278 = ripilvirine; TPV = tipranavir; ZDV = zidovudine

Criteria Used for Recommendations

In general, Panel recommendations are based on review of pediatric and adult clinical trial data published in peer-reviewed journals. (The Panel may also review data prepared by manufacturers for Food and Drug Administration [FDA] review and data presented in abstract format at major scientific meetings.) Few randomized, Phase III clinical trials of 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 nonrandomized, 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 cell count and HIV RNA levels. The Panel continually modifies recommendations on the optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities become recognized.

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

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size and number;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions 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 not available or are 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

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	• Similar resistance profile and no additive benefit	• No exceptions.
• d4T ***plus*** ZDV	• Antagonistic effect on HIV	• 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 the risk.
Unboosted SQV, DRV, or TPV	• Poor oral bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions.

Key to Acronyms: 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

appropriate for consideration in the management of the treatment-experienced child, even though they are not recommended for initial therapy in children (see Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

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 10–13. In addition, because ART will need to be administered lifelong, considerations related to the choice of initial 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 following assessment and counseling of the caregivers regarding adherence to therapy[3, 18].

Choice of NNRTI- Versus PI-Based Initial Regimens

Preferred regimens for initial therapy include both NNRTI- and PI-based regimens. The selection of an NNRTI- or PI-based regimen should be based on patient characteristics and preferences, results of viral 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, age 2 to 35 months, in seven 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[1]. 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[2]. 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[19-21].

A comparison of a PI-based regimen and an NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children, age 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 age >3 years. After 4 years, 82% of children in both groups 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 age <2.8 years); PENPACT-1 generally enrolled older children[22].

Results of the P1060 study support the recommendation that a PI-based regimen containing lopinavir/ritonavir should be the recommended, preferred initial regimen for children <3 years of age 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 a better

immunologic response and growth compared with children 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 compared with children continuing a lopinavir/ritonavir regimen[23]. Based on these findings, the potential for improved lipid profiles with nevirapine use[23-24], and the poor palatability of liquid lopinavir/ritonavir, liquid nevirapine remains an acceptable alternative for infants not exposed to single-dose nevirapine for PMTCT who cannot tolerate lopinavir/ritonavir.

In children >3 years of age, 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 approved pediatric indication. Nevirapine is available in a liquid formulation, but efavirenz is not available in a liquid formulation in the United States. Advantages and disadvantages of different NNRTI drugs are delineated in Table 10. 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. Additionally, 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 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 compared with lopinavir/ritonavir-based regimens[1-2]. 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. NNRTIs, similar to PIs, have the potential for interactions 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 two NRTIs, is the preferred NNRTI for initial therapy of children age ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no randomized studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome (SJS) and rare but potentially life-threatening hepatitis[25-26], nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of ARV-naive 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[27]. In randomized controlled trials in treatment-naive adults, efavirenz-treated patients had superior or similar virologic activity compared with patients receiving PI- or triple NRTI-based regimens[28-31]. Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below)[32-36]. In PENPACT-1 (PENTA 9/PACTG 390) subjects receiving efavirenz or nevirapine showed comparable virologic suppression after 4 years[22]. An analysis of children and adults starting first-line ART in Uganda has demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years)[37]. Few had received nevirapine as part of a PMTCT regimen.

Efavirenz in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children[38-44]. Results are comparable to those seen in adults. At this time, no pediatric formulation of efavirenz is available in the United States. The appropriate dose of efavirenz for children age <3 years has not been determined; therefore, efavirenz is not recommended for children in this age group. For children ≥3 years of age who are unable to swallow pills, some clinicians recommend breaking open efavirenz capsules and adding the contents to food or liquid. However, because data on the PKs of efavirenz administered in this manner are lacking, this practice is not recommended.

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults; reported side effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after initiating efavirenz. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in adult patients with higher levels of drug[45-48]. 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[42, 44]. Additionally, efavirenz taken by a pregnant woman during the first trimester of pregnancy is potentially teratogenic to the fetus (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Efavirenz is not recommended for initial therapy in adolescent females who are sexually active and may become pregnant unless adequate contraception can be ensured.

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)[49]. Nevirapine in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children[50-52].

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)[36]. Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens[53]. Additionally, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 counts and in women, particularly women with CD4 counts >250 cells/mm^3 and men with CD4 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 (LFTs) and not CD4 count at the time of nevirapine initiation[54]. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults[51-52, 55]. 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 prior to adolescence[55]. 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[56]. In contrast, skin reactions and HSRs associated with nevirapine use have been reported in children[57]. 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[58].

Because of the higher potential for toxicity and possibly an increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children age ≥3 years. In children <3 years, nevirapine is considered an alternative NNRTI 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 compared with infants on lopinavir/ritonavir-based regimens [1-2, 19, 59]. However, infants treated with nevirapine showed a trend for greater improvements in both immunologic status and growth[1].

A recent study randomized infants exposed to nevirapine who had achieved viral suppression for an average of 9 months using a lopinavir/ritonavir-based therapy as part of a PMTCT regimen to continue the lopinavir/ritonavir regimens or to switch to a nevirapine-based regimen. After 52 weeks of follow up, plasma viremia ≥50 copies/mL (the primary endpoint) occurred less frequently in the switch group compared with the continuing arm. CD4 response was also better in the switch group. However, 20% of the switch 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[60]. These findings suggest this strategy may be an option for children in whom standard genotyping before treatment detects no NNRTI mutations and should be undertaken with careful monitoring of viral load[23].

Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4 counts >250/mm^3 because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk[26]. Nevirapine also should be used with caution in children with elevated pretreatment LFTs.

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

Summary: PI-Based Regimens

Nine PIs are currently approved for use; seven are approved for use in children and have pediatric drug formulations. Advantages and disadvantages of different PIs are delineated in Table 11. 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 and may 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 11 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, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children age >6 weeks[61] and for atazanavir, fosamprenavir, darunavir, and tipranavir with low-dose ritonavir in children age ≥6 years. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia[62] and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated lopinavir/ritonavir as

Table 10: Advantages and Disadvantages of Different NNRTIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children
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	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 ≥3 years of age who can take capsules)	• Potent ARV activity. • Once-daily administration. • Can give with food (but avoid high-fat meals).	• Neuropsychiatric side effects (bedtime dosing recommended to reduce CNS effects). • Rash (generally mild). • No commercially available liquid. • No data on dosing for children age <3 years. • Teratogenic in primates. Use with caution in adolescent females of childbearing age.
Alternative		
NVP	• Liquid formulation available. • Dosing information for young infants available. • Can give with food.	• Reduced virologic efficacy in young infants, regardless of whether exposed 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 autoinduction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing.
Not Recommended		
EFV (for children age <3 years)	• Potent ARV activity. • Once-daily administration. • Can give with food (but avoid high-fat meals).	• Neuropsychiatric side effects (bedtime dosing recommended to reduce CNS effects). • Rash (generally mild). • No commercially available liquid. • No data on dosing for children age <3 years. • Teratogenic in primates. Use with caution in adolescent females of childbearing age.

Table 10: Advantages and Disadvantages of Different NNRTIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 2

	Advantages	Disadvantages
Not Recommended		
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.
Rilpivirine	• Once-daily administration. • Reduced CNS effects compared with EFV.	• No data on pediatric dosing or safety. • No pediatric formulation available. • Higher rate of treatment resistance and cross resistance to the NNRTI class in adults compared with EFV. • Adults with viral loads >100,000 copies/mL) are more likely to experience virologic failure compared with patients with viral loads <100,000 copies/mL.

Key to Acronyms: 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

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 ≥42 weeks postmenstrual age and 14 days of age, at the current time atazanavir with low-dose ritonavir should be used only in children ≥6 years of age. Two additional PIs, darunavir and fosamprenavir, can be considered as alternative PIs for use in children age ≥6 years when 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 age ≥2 years, atazanavir without boosting ritonavir in adolescents age ≥13 years and who weigh >39 kg, and nelfinavir in children age ≥2 years. A saquinavir/ritonavir (1,000/100 mg twice daily)-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults[63]. The guidelines for adults and adolescents list the saquinavir / ritonavir-based regimen as an acceptable PI-based regimen that should be used with caution as initial therapy[26]. 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[64-67]. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults[64, 67]. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial

therapy in children. Additionally, tipranavir is not recommended for initial therapy at the present time because experience with the drug in treatment-naive children is limited.

Because the data on PKs of full-dose dual-PI combination regimens in children (e.g., saquinavir plus co-formulated lopinavir/ritonavir or plus nelfinavir) are limited[68-70], these combinations are not recommended as initial therapy in children.

Preferred PIs

Atazanavir with low-dose ritonavir as preferred PI (for children ≥6 years) (AI*): Atazanavir is a once-daily PI that was approved for use in children >6 years of age in March 2008. It has equivalent efficacy to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naive adults[71-72]. 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[73]. Among 41 treatment-naive children ages 6–18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 68% and 59% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 48 weeks[74]. When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children >6 years of age[75-76] and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting[77]. 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[62].

Lopinavir/ritonavir as preferred PI (AI): In clinical trials in adults, regimens containing lopinavir/ritonavir plus two 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 superior virologic efficacy compared 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[78-79]. 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[1, 7, 80-85]. (See Appendix A: Pediatric Antiretroviral Drug Information for detailed information.) In addition, dosing and efficacy data in infants as young as 4 weeks of age are available[7, 61, 80]. Post-marketing reports of lopinavir/ritonavir-associated cardiac toxicity (including complete atrioventricular [AV] 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. Additionally, although once-daily lopinavir/ritonavir is FDA approved for initial therapy in adults, PK data in children do not support a recommendation for once-daily dosing in children[86-87].

Alternative PIs

Darunavir with low-dose ritonavir as alternative PI (for children age ≥6 years) (AI*): Darunavir combined with low-dose ritonavir is approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children age ≥6 years. In a randomized, open-label trial in adults, darunavir/ritonavir

(800/100 mg once daily) was found to be noninferior 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 in 78% of lopinavir/ritonavir recipients (p <0.001). Adverse events were also less common in the darunavir/ritonavir group (p <0.01)[88]. No published data exist on the use of darunavir as part of initial treatment in children or the use of once-daily darunavir in children. In a study of treatment-experienced children (6–17 years of age), twice-daily darunavir/ritonavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks[89]. Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from one study in treatment-experienced children and the finding of high potency and low toxicity in adults. Some experts would only recommend boosted darunavir for treatment-experienced children and reserve its use for patients with PI-resistant mutations. Once-daily dosing of darunavir is not recommended for children.

Fosamprenavir with low-dose ritonavir as alternative PI (for children age ≥6 years) (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 approved for use in pediatric patients ≥2 years of age. The approval was based on two open-label studies in pediatric patients 2–18 years of age[90-91]. 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[92]. In children age ≥6 years, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. Data on appropriate dosing of fosamprenavir in combination with low-dose ritonavir in children age <6 years are not available; therefore, this combination cannot be recommended for children in that age group. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

PIs for Use in Special Circumstances

Atazanavir without ritonavir boosting in children age ≥13 years (BII*): Although unboosted atazanavir is approved for treatment-naive adolescents age ≥13 years who weigh >39 kg and are unable to tolerate ritonavir, data from the ongoing IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m^2 body surface area basis) are required in adolescents than in adults to achieve adequate drug concentrations. (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[93]. 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 age ≥2 years (BII*): Fosamprenavir without ritonavir boosting has been studied in children age ≥2 years but is only recommended in special circumstances when preferred or alternative PI-based regimens cannot be used.

Nelfinavir for children age ≥2 years (BI*): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children age ≥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[94]. The drug has been well tolerated—diarrhea

is the primary side effect of the drug; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression of 26%–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[95]. In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus in 80% of children with therapeutic nelfinavir troughs (>0.8 mg/L)[95]. The interpatient variability in plasma concentrations is great in children, with lower levels in younger children[96-101]. The optimal dose of nelfinavir in younger children, particularly in children age <2 years, has not been well defined. In one study, infants required higher doses of nelfinavir (relative to body size) than older children to achieve adequate drug levels[96]. PK parameters in adolescent patients have not been well studied, and some adolescents may require higher nelfinavir doses than those recommended in adults. 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[79, 102-105], make nelfinavir an agent for use in special circumstances in treatment-naive children age ≥2 years and not recommended for treatment of children age <2 years.

The pediatric powder formulation of nelfinavir has a poor acceptance rate when mixed with food or formula, and the PKs of the drug are extremely variable in children. To overcome the problems associated with this formulation, tablets are dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable PK parameters in a study in adults[106].

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 1 of 4

	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 age ≥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).

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 4

	Advantages	Disadvantages
Preferred		
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 age ≥6 years	• Effective in PI-experienced children when given with low-dose RTV boosting.	• Pediatric data limited to ARV-experienced children. • Pediatric pill burden high with current tablet dose formulations. • No liquid formulation. • Food effect (should be given with food). • Must be given with 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 (investigation ongoing).
FPV in combination with low-dose RTV in children age ≥6 years	• 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.
Use in Special Circumstances		
ATV (unboosted) in treatment-naive adolescents age ≥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 age ≥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.

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 3 of 4

	Advantages	Disadvantages
Use in Special Circumstances (continued)		
NFV in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food). • Can give with food. • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate.	• Diarrhea. • Powder formulation poorly tolerated. • Food effect (should be administered with food). • Appropriate dosage for younger children not well defined. • Need for 3 times daily dosing for younger children. • Adolescents may require higher doses than adults. • Less potent than boosted PIs.
Not Recommended		
ATV (unboosted) in children age <13 years and/or weight <39 kg	• Once-daily dosing (age >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)	• May 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.
RTV (full dose as single PI)	• Liquid formulation. • Can be given with food.	• Poor palatability of liquid (bitter taste). • GI intolerance. • Food effect (should be administered with food). • Large number drug interactions (most potent inhibitor of CYP3A4).
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.

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 4 of 4

	Advantages	Disadvantages
Not Recommeded (continued)		
NFV in children age <2 years	• Powder formation (for liquid preparation or to be added to food). • Can give with food. • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI- containing regimens in older patients where the adult dose is appropriate.	• Diarrhea. • Powder formulation poorly tolerated. • Food effect (should be administered with food). • Appropriate dosage for younger children not well defined. • Need for 3 times daily dosing for younger children. • Adolescents may require higher doses than adults. • Less potent than boosted PIs.
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

Key to Acronyms: 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

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

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, six NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA approved for use in children <13 years of age. Tenofovir is FDA approved for use in adolescents who are ≥12 years of age and weigh ≥35 kg. Dual-NRTI combinations form the "backbone" of combination regimens for both adults and children. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; and emtricitabine in combination with stavudine or didanosine[18, 40, 94, 100, 107-108]. Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 12.

Preferred Dual-NRTI Regimens

The dual-NRTI combinations preferred for initial therapy in children are abacavir or zidovudine combined with either lamivudine or emtricitabine.

Zidovudine in combination with either lamivudine or emtricitabine in children (AI*): The most extensive experience in children is with zidovudine in combination with lamivudine. 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

Table 12. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 1 of 2

	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/heavier 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/heavier 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 ≥12 years of age and Tanner Stage 4 or 5 only	• 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/heavier patients.	• No pediatric formulation of TDF. • 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 compliance 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 ≥12 years of age and 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.	• No pediatric formulation of TDF. • 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.
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 less palatable than 3TC or FTC liquid formulation. • Food effect (recommended to take ddI 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when compliance is an issue.

Table 12. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 2

	Advantages	Disadvantages
Use in Special Circumstances		
d4T ***plus*** (3TC ***or*** FTC)	• Moderate pediatric experience. • Palatable liquid formulations. • Can give with food. • FTC 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 adolescents ≥12 years of age and Tanner Stage 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.	• No pediatric formulation of TDF. • 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 may 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.
TDF-containing regimens in children <12 years of age or children ≥12 years who are Tanner Stage 1	• Resistance slow to develop. • Once-daily dosing for TDF (adults). • Less mitochondrial toxicity than other NRTIs. • Can give with food.	• No pediatric formulation of TDF. • Limited pediatric experience. • Potential for bone and renal toxicity; bone toxicity appears to be more frequent in younger children. • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
ZDV ***plus*** d4T	• None.	• Pharmacologic and antiviral antagonism.

Key to Acronyms: 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

and neutropenia; minor toxicities include gastrointestinal (GI) toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few side effects. Although there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir 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[109-110].

Abacavir in combination with either lamivudine or emtricitabine in children (AI): Abacavir in combination with lamivudine has been shown to be as potent or, possibly, more potent than zidovudine in combination with lamivudine in both children and adults[111-112]. 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[112]. 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%)[113]. 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%)[114]. 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 in combination with either lamivudine or emtricitabine in children ≥ 12 years and Tanner Stage 4 or 5 (AI*): Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation[115-118]. The use of tenofovir in pediatric patients age 12 to <18 years was recently approved by the FDA based on data from 1 (unpublished) randomized study in 87 treatment-experienced subjects who 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.

Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents age ≥12 years and Tanner Stage 4 or 5. 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[119-120]. 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 times to virologic failure and to first adverse event were both significantly shorter in patients randomly assigned to abacavir/lamivudine than in those assigned to tenofovir/emtricitabine. Results for patients with lower entry viral loads and for comparisons by assignment to efavirenz or boosted atazanavir are not yet available[121]. 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[122]. 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

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

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety.
Insufficient Data to Recommend		
RAL	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Limited data on pediatric dosing or safety. • Pediatric formulations are investigational. • Potential for rare systemic allergic reaction or hepatitis.

Key to Acronyms: ARV = antiretroviral; RAL = raltegravir

adults[123]. 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[124].

In some, but not all, studies, decreases in bone mineral density (BMD) have been observed in both adults and children taking tenofovir for 48 weeks[115-118, 125]. 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 1–3, for whom the risk of bone toxicity may be greatest[115, 118]. (See Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information.) Renal toxicity has been reported in children and adults receiving tenofovir. In 1 single-center study, the rate of beta-2-microglobulinuria was higher in children receiving tenofovir (12 of 44 children) than in children receiving other ARV agents (2 of 48 children), although creatinine clearance (CrCl) did not differ between the groups[126]. 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 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 adolescents ≥12 years and 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[127]. 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[100, 112].

The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children age 3-21 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[40]. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who must be fed frequently and 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[128]. To improve compliance, 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 preferred that didanosine be administered 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 and tenofovir in combination with lamivudine or emtricitabine in adolescents age ≥12 years and Tanner Stage 2 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[129-131]. Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations[127]. In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferred to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

Dual-NRTI Regimens Not Recommended for Use

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[107-108, 132]. 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[133-134]; additionally, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy[129, 135]. Abacavir/didanosine, abacavir/tenofovir, and didanosine/tenofovir are not recommended as dual-NRTI backbones in initial therapy on the basis of insufficient data in children.

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%−50% have been reported[136-137]. 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 (e.g., 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 equivalent virologic efficacy compared with indinavir-[138] or nelfinavir-containing regimens[139] but was inferior to an efavirenz-based regimen[28, 140]. 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[141].

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[142-143]. 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[144-146]. The tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults; however, no comparative data are available and the regimen is not recommended[147].

Regimens Not Recomended 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[41-43].

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 (an integrase inhibitor), tenofovir (in children age <12 years), and etravirine and ripilvirine (both NNRTIs). Raltegravir is being evaluated in treatment-experienced children; however, PK, safety, and efficacy data are not yet available and no pediatric formulation is commercially available. In June 2008, FDA approved tipranavir boosted with ritonavir for use in treatment-experienced children age 2–18 years; however, data are insufficient to consider use of the agent for initial therapy.

Enfuvirtide, a fusion inhibitor, is approved for use in combination with other ARV drugs to treat children age ≥6 years who have evidence of HIV replication despite ongoing ART (i.e., 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 never 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 the 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 infant born to 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[26].

In a child with treatment failure associated with drug resistance and persistent nonadherence, monotherapy using an interim "bridging" regimen of lamivudine alone may be considered. "Bridging" regimens have been reported to be effective in delaying immunologic decline in adults with failing combination therapy, often due to nonadherence[148-149]. Bridging regimens should not be considered as initial therapy and should only be used in the interim as the clinician works intensively with the patient and caregivers to improve adherence before initiating a new, suppressive combination ARV 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 the 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 an NNRTI to the regimen. However, a child remaining on a dual-NRTI regimen should be switched to a three or more drug combination if viral rebound occurs (see Antiretroviral Treatment Failure in 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 pharmacological 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[36].

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[144-146].

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Monitoring of Children on Antiretroviral Therapy (Updated August 11, 2011)

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

Children who initiate 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 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 the child and caregivers need assistance in determining whether the effects are temporary and can be tolerated or whether they are more serious or long-term and necessitate a visit to the clinician. Thus, it is prudent for the clinician to assess the child within 1–2 weeks of initiating therapy, either in person or with a phone call, to assure proper administration of medications and to evaluate clinical concerns. Many clinicians will plan additional contact (in person or over the telephone) with the child and 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 will allow for honest report(s) and ensure dialogue between the provider and both the child and the caregiver(s), even with those who report inconsistent medication adherence.

Baseline laboratory assessments including CD4 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 (UA), and serum lipid evaluation (cholesterol, triglycerides [TGs]) should be done before initiation of therapy. In addition, a baseline assessment of ARV resistance using a genotype assay is recommended (see Antiretroviral Resistance Testing). Within 4–8 weeks after initiating or changing therapy, the child 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, HIV RNA test) 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. Following 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 4–8 weeks of therapy.

Subsequently, children taking ARV medication should have assessments of medication adherence and regimen toxicity and effectiveness at least every 3−4 months. For children and youth who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2–3 years, some experts monitor CD4 counts and HIV RNA levels less frequently. Table 15 provides one proposed monitor-

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

	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
Resistance Testing	X							X
Adherence evaluation			X	X	X	X		X
Lipid panel	X		X				X	
Urinalysis	X		X				X	

[1] In the event that initiation of therapy is within 30-45 days of a Monitoring Pre-Therapy lab result, repeating at initiation may not be necessary.

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

[3] For children who are in a stable treatment status (non-detectable HIV RNA and normal CD4 count/% 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 (eg to review adherence and update dosing for interim growth).

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

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

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

ing schedule, which will require adjustment based on the specific therapy the child is receiving. Assessments should include basic hematology, chemistry, CD4 count/percentage, and HIV viral load. Monitoring of drug toxicities should be tailored to the particular medications the child is taking; for example, periodic monitoring of 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 (e.g., 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 <40–80 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 are often detected in adults (and children) on ART and should not be considered "virologic failure." For definitions and management of virologic treatment failure, see Antiretroviral Treatment Failure in Infants, Children, and Adolescents.

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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated August 11, 2011)

Panel's Recommendations
• Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent. Adolescents with perinatal infection generally have a very different clinical course and treatment history than those who acquired HIV during adolescence **(AIII)**. • Appropriate dosing of antiretroviral (ARV) medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and physiologic development **(AII)**. • Effective and appropriate contraceptive methods for adolescence should be selected to reduce the likelihood of unintended pregnancy and to prevent transmission of HIV to sexual partners **(AI)**. • Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**. • Efavirenz should not be used by an adolescent female who desires to become pregnant or who does not use effective and consistent contraception **(AII)**. Efavirenz also should not be used throughout the first trimester of pregnancy **(AII)**. • Pediatric and adolescent care providers should prepare adolescent patients for the transition into adult care settings **(AIII)**.

Background

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive ARV treatment history[1]. Adolescents with behaviorally acquired infection (i.e., infection acquired via sexual activity or intravenous substance use) generally follow a clinical course similar to that in adults. Because behaviorally infected adolescents are at an early stage of HIV infection, 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 (PKs), 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 (OIs) traditionally have been 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 (Tanner Stages 1 and 2) are administered doses using pediatric schedules, whereas those in late puberty (Tanner Stage 5) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug PKs. Puberty may be delayed in children who were infected with HIV perinatally[5], adding to discrepancies between Tanner stage-based dosing and age-based dosing, although delayed onset of puberty appears to be uncommon in children receiving potent combination therapy[6].

Many ARV medications (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 scaling of adult doses, 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 medication for 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. Many factors may affect the transition from pediatric to adult doses. In addition to toxicity, pill burden, adherence, and virologic and immunologic parameters, factors may include social determinants, such as housing, family support, employment, and recent discharge from the foster care system.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents with HIV infection, regardless of mode of acquisition, may be sexually active. Contraception methods and safer sex techniques for prevention of HIV transmission should be discussed with them regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use)[7].

The possibility of planned or unplanned pregnancy should be considered when selecting an ARV regimen for the adolescent female. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans including preconception care, and use of effective contraception should be discussed with the patient. In addition, concerns about specific ARV drugs and birth defects should be addressed immediately to preclude misinterpretations or lack of adherence for adolescents with unexpressed plans for pregnancy. Adolescent females who are trying to conceive or who are not using effective and consistent contraception should avoid efavirenz-containing regimens because of the potential for teratogenicity with fetal exposure to efavirenz in the first trimester.

Contraceptive-Antiretroviral Drug Interactions

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents available at http://aidsinfo.nih.gov)[8]. These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving ARV drugs with such interactions. Whether interactions with ARV drugs would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot methoxyprogesterone 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 among women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional side effects, and no clinically significant changes in ARV drug levels[9-10]. At this time concerns about bone mineral loss with long-term use of DMPA with or without ART (specifically tenofovir)[11] should not preclude use of DMPA as an effective contraceptive. However, more diligent monitoring of bone mineral density (BMD) in young women on DMPA may need to be considered[11]. Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). 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 desire to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with ART use during pregnancy (see Health and Human Services [HHS] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States available at http://aidsinfo.nih.gov)[12].

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 to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant adults or adolescents. Details regarding choice of ARV 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[12]. Although information about the pregnancies of adolescents who were infected with HIV perinatally is limited, outcomes in this population appear similar to outcomes in adult cohorts[13-16].

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 adolescents infected with HIV. Transition is described as "a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system"[17]. 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, the adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers who often do not have a long-standing relationship with the adolescent. Providing the adolescent and the 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 the pediatric and adult provider to share joint care of the patient for a period of time. Providers should also have a candid discussion with the transitioning adolescent to understand what qualities the adolescent considers most important in a provider (e.g., confidentiality, small clinic size, after-school appointments). Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care. Some general guidelines about transitional plans and who might best benefit from them are available[18-20].

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated August 11, 2011)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again prior to 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 (e.g., quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load **(AII)**. • When feasible, once-daily antiretroviral (ARV) regimens should be prescribed **(AI*)**. • To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with the patient/caregiver, and identify mutually acceptable goals for care **(AII*)**.

Background

Medication adherence is fundamental to successful ART. Adherence is a major factor in determining the degree of viral suppression achieved in response to ART[1-4]. Poor adherence can lead to virologic failure. Prospective adult and pediatric studies have shown the risk of virologic failure to increase as the proportion of missed doses increases[2, 5-6]. 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 and drug class as well as pattern of adherence[7]. Viral suppression can be achieved with lower levels of adherence when using boosted PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens[7-9]. Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy depending on the drug combination[10].

Subtherapeutic ARV drug levels resulting from poor adherence may facilitate the development of drug resistance to one or more drugs in a given regimen and possible cross resistance to other drugs in the same class. Multiple factors, including regimen potency, pharmacokinetics (PKs), 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 for patients who develop drug-resistant viral strains.

Evidence indicates that adherence problems occur frequently in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics[3-4, 12-17]. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial characteristics of the child and parent, have been associated with adherence; however, no clear predictors of either good or poor adherence in children have been consistently identified[12, 14, 18-23]. Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment[6, 24]. 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[21-22]. Limited availability of palatable formulations for young children is especially problematic[5, 25]. Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments as well as the ability and willingness of the child to take the drug. Barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal of medications[26]. Some caregivers may place too much responsibility for managing medications on older children before the children are developmentally able to take on such tasks[27]. Many other barriers to adherence exist for children with HIV infection. For example, caregivers' unwillingness to disclose the child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling 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.

Specific Adherence Issues for Adolescents

HIV-infected adolescents also face specific adherence challenges[18, 28-30]. Several studies have identified pill burden as well as lifestyle issues (i.e., not having medications on hand when away from home, change in schedule) as barriers to complete adherence[18, 28]. Adolescents' denial and fear of their HIV infection is common, especially in recently diagnosed youth; 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 can all 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 has also been identified as a barrier to adherence in adolescents[31]. Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, may have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness because they lack familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease stage all correlate with nonadherence[29, 32]. In a study of 833 HIV-infected Medicaid beneficiaries 12–17 years of age, 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[33]. In a cross-sectional study of youth with perinatal HIV infection, no significant differences in the frequency of mental health disorders were found between adherent and nonadherent participants[34]. A review of published papers on adherence among HIV-infected youth, however, suggests that depression and anxiety have been consistently associated with poorer adherence[32]. 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 ARV treatment have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers and alarm devices, are well accepted by some youth. Small, 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[35]. Another study evaluating the efficacy of a four-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months among youth taking ART. However, reduction in viral load was not maintained at 9 months[36].

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 ARV treatment initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by the child and family and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership with the 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 the patient's explicit agreement with the treatment plan, including strategies to support adherence. Also, it is important to alert patients to the 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[17, 37-39]. Both caregivers and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multidrug-resistant virus. Other measures include quantitative self-report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed[40]. Also, targeted questions about stress, pill burden, and daily routine are recommended[12, 18, 37]. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports[41]. Electronic monitoring devices, such as Medication Event Monitoring System (MEMS) caps, which are equipped with a computer chip that records each opening of a medication bottle[42], have been shown to be useful tools to measure adherence in some settings[41, 43-44]. 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[45-46]. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring (TDM), may be a useful method to identify nonadherence[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 atti-

tude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both the HIV-infected child and caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources[48-49].

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 (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers rather than one specific intervention may be most effective[27, 50-53]. 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[54-58]. 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[53]. However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that DOT was no more effective than self-administered treatment[59]. 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[60]. Table 16 summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

Regimen-Related Strategies

Highly active ARV regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects[61]. When nonadherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it may be simplified. For example, when the burden of pills is great, one or more drugs can be changed to result in a regimen containing fewer pills and potentially greater adherence. When feasible, once-daily regimens should be prescribed. Several studies in adults have demonstrated better adherence in once-daily compared with twice-daily ARV regimens[62-65]. 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 may be masked by a small amount of flavoring syrups or food (see Appendix A: Pediatric Antiretroviral Drug Information) or the child may be taught to swallow pills in order to overcome medication aversion[66].

Child/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient/caregiver education. Educating families about adherence should begin before 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 the 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 the HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence[67-68]. Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children 4 to 21 years of age[69]. Availability of mental health services and treatment of mental health disorders may also facilitate adherence to complex ARV regimens. For nonadherent children who are at risk of disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered[70]. If adequate resources are available, home nursing interventions may also be beneficial[71]. Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children[59-60, 72], 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.

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with the families. This process begins early in the provider's relationship with the family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important[73-75]. Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child centered and includes caregivers in adherence support has also been shown to improve treatment outcomes[76].

Table 16. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care with patient and caregiver.
• Obtain explicit agreement on need for treatment and adherence with patient and caregiver.
• 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 prior to 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 (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent).
• Develop a treatment plan that the patient and family understand and to which they feel committed.
• Establish readiness to take medication by practice sessions or other means.
• Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency and number of pills.
• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.
• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
• Assess pill-swallowing capacity and offer pill-swallowing training.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties 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 or telephone calls to support and assess adherence.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support **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 (Updated August 11, 2011)

Panel's Recommendations
• If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately **(AIII)**. Once the symptoms of toxicity have resolved, antiretroviral therapy (ART) should be resumed with substitution of a different antiretroviral (ARV) drug or drugs for the offending agent(s) **(AII*)**.
• When changing therapy because of toxicity or intolerance to a specific drug in a virally suppressed child, changing a single 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*)**.

Side effects or intolerance of ARV agents often occur and should prompt a re-evaluation of the ARV regimen. Drug-related toxicity may be acute, occurring soon after a drug has been administered; subacute, occurring within 1−2 days of administration; or late, occurring after prolonged drug administration. The differential diagnosis of drug toxicity includes toxicity due to HIV infection or other infections or conditions, for example, bone marrow suppression with disseminated *Mycobacterium avium* complex (MAC) infection or anemia due to blood loss from cytomegalovirus (CMV) colitis. ARV drug-related adverse events may 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 the patient's virus. Knowledge of the patient's ARV history and viral resistance profile prior to the current course of ART is essential. Any new agent used should be assessed for likely effectiveness against the 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).

The physician, patient, and caregiver should discuss the response to a medication-related toxicity, taking into account the severity of toxicity, the relative need for viral suppression, and the available 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 the initiation of therapy, at regular provider visits, and at onset of any side effect. Common, self-limited side effects should be anticipated. For example, when initiating therapy with boosted protease inhibitors (PIs) many patients may experience gastrointestinal (GI) side effects such as nausea, vomiting, diarrhea, and abdominal pain. Instructing the patient to take PIs with food may help minimize these side effects. For some patients antiemetics and antidiarrheal agents may be required for symptom management. Central nervous system (CNS) side effects are commonly encountered when initiating therapy with efavirenz. Symptoms may include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime to help minimize these

side effects and be advised that these side effects should diminish or disappear within 2–4 weeks of initiating therapy. In addition, for mild rash, symptomatic treatment such as antihistamines may be given. For some moderate toxicities, substituting the toxicity-associated ARV drug with a drug in the same drug class but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required. Severe, life-threatening toxicity requires discontinuation of all ARV drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity). Another drug can be substituted for the drug associated with the toxicity once the patient is stabilized and the toxicity is resolved.

When a patient experiences an unacceptable adverse effect from ART every attempt should be made to identify the offending agent and replace the drug with another effective agent as soon as possible[1-2]. For example, if therapy needs to be stopped due to 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 starting them one at a time and observing for adverse effects. Many experts recommend stopping efavirenz or nevirapine several days before stopping other drugs, if possible, because these drugs have significantly longer half-lives than nucleoside reverse transcriptase inhibitor (NRTI) ARV drugs. However, if a patient has a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

When therapy is changed because of toxicity or intolerance in the context of virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible[3-7]. 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 option. However, when therapy is changed in a patient because of virologic failure, substitution of a single active agent for a single drug in a multidrug regimen is generally not recommended because of concern for development of resistance (see Approach to the Management of Antiretroviral Treatment Failure).

TDM is not available on a routine basis to most clinicians, and the settings in which TDM is useful are unclear, especially in children. One such setting, however, may be in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In this situation, it is reasonable for the clinician to use TDM (if available) to determine if the toxicity is due to a concentration of drug exceeding the normal therapeutic range[8-9]. 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 the patient's virus is sensitive (e.g., change to abacavir for zidovudine-related anemia or to nevirapine for efavirenz-related CNS symptoms).
- Change drug class, if necessary (e.g., from a PI to a non-nucleoside reverse transcriptase inhibitor [NNRTI] or vice versa) and if the patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

Tables 17a–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, and hypersensitivity reactions (HSRs) 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

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 initiation of 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 • Age <14 days (whether premature or term) • Low birth weight	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.
Neuropsychiatric symptoms and other CNS manifestations	EFV	**Onset:** 1–2 days after initiation of EFV 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 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 **Adults:** >50% for any CNS manifestations of any severity 2% for EFV-related severe CNS manifestations **Children:** 15%–20% for any EFV-related CNS manifestations	• Insomnia correlated 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 may 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. Reduce dose or use alternative drug if EFV trough level ≥4 mcg/mL.
	RAL	**Presentation:** Headaches, insomnia	**Adults:** <5% in adult trials **Children:** no pediatric data available	• Elevated RAL concentrations • Prior history of insomnia		Consider a trial of drug discontinuation for severe insomnia.
Intracranial hemorrhage	TPV	**Onset:** 1–513 days after starting TPV	**Adults:** In premarket approval data in adults, 0.23/100 patient-years **Children**: No case of ICH yet reported in children	• Unknown; possibly prior history of bleeding disorder	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, recent neurosurgery.	Discontinue TPV in case of suspicion of ICH.

Key to Acronyms: ARV = antiretroviral; CNS = central nervous system; CYP450 = cytochrome P450; EFV = efavirenz; LPV/r = lopinavir/ritonavir; RAL = raltegravir; TDM = therapeutic drug monitoring; TPV = tipranavir

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Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Dyslipidemia	**PIs:** All PIs; lower incidence with ATV **NRTIs:** Especially d4T	**Onset:** Weeks to months after beginning therapy **Presentation:** *PIs:* ↑LDL-C, TC, and TG *NNRTIs:* ↑LDL-C, TC, and HDL-C *NRTIs:* ↑LDL-C, TC, and TG	20%–50% of children receiving cART 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, smoking cessation **Monitoring:** *Adolescents and adults:* Obtain fasting (12-hour) before initiating or changing ARV therapy, then every 3–6 months, and thereafter, every 6–12 months. *Children without lipid abnormalities or CVD 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) 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 anti-hyperlipidemic agents.	Counsel lifestyle modification (low-fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). Switch to a new ARV regimen less likely to cause lipid abnormalities.* **Pharmacologic Management:** Initiate drug therapy promptly in patients with TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin†. Fibrates such as gemfibrozil and fenofibrate may be used as alternative agents for adults with ↑TG but are not approved for use in children. N-3 PUFAs derived from fish oils. No consensus as to what LDL-C should prompt treatment in children receiving ARVs ‡. *Patients at high risk for CVD:* Goal LDL-C ≤100 mg/dL. *Patients at moderate risk for CVD:* Goal LDL-C ≤130 mg/dL. *Patients at risk for CVD:* Goal LDL-C ≤160 mg/dL.

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

† Statins are teratogenic and should not be used in 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. Multiple drug interactions exist between lipid-lowering agents and ARVs.

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

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

Rosuvastatin (Crestor)
Ages 10–17 years: 5–20 mg once daily

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

Key to Acronyms: ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; cART = combination antiretroviral therapy; CK = creatine kinase; CVD = cardiovascular disease; d4T = stavudine; HDL-C = 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; TC = total cholesterol; TG = triglycerides

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Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ vomiting	Principally ZDV and PIs (e.g., 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	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, may be useful in extreme or persistent cases.
Diarrhea	PIs (NFV, LPV), buffered ddI	**Onset:** Early **Presentation:** Generally soft, more frequent stools	Varies with antiretroviral agent. 10%–30% in some series.	Unknown	Generally improves with time; 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, d4T (especially with concurrent use); 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 (e.g., 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; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

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Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia*	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 disease • Neonatal blood loss • Concurrent ZDV + 3TC neonatal prophylaxis **HIV-infected children on ARVs:** • Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) • Poorly controlled HIV • Marrow-toxic drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency	**HIV-exposed newborns:** Monitor CBC at birth. Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., born prematurely, 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 gm/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†). **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.
Neutropenia*	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 Higher with ZDV-containing regimens	**HIV-exposed newborns:** • *In utero* exposure to ARVs • Concurrent ZDV + 3TC neonatal prophylaxis **HIV-infected children on ARVs:** • Poorly controlled HIV infection • Marrow-toxic drugs (e.g., 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/uL or, if 4 weeks or more of 6-week ZDV prophylaxis regimen are already completed, discontinuing ARV prophylaxis entirely (see Perinatal Guidelines†). **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.

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

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

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARVs = antiretrovirals; 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

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. NRTIs, especially ZDV, ddI, d4T, may be associated with lactic acidosis and hepatic steatosis. Rarely, prolonged exposure to ddI is associated with non-cirrhotic portal hypertension with esophageal varices. AST, ALT elevations while on NVP or ABC may be associated with skin rash or an HSR. HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, TDF.	Uncommon in children Frequency varies with different agents and drug combinations	• HBV or HCV coinfection • Elevated baseline ALT, AST • Other hepatotoxic medications • Alcohol use • Underlying liver disease For NVP-associated hepatic events in adults: • pre-NVP CD4 count >250 cells/mm^3 in female • pre-NVP CD4 count >400 cells/mm^3 in male • 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 (e.g., HBV or HCV coinfected, have 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 NVP (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, NRTIs, ZDV, d4T, ddI in particular (see also lactic acidosis). Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.
Indirect hyperbilirubinemia	IDV, ATV	**Onset:** Early in therapy. **Presentation:** Jaundice. Asymptomatic elevation of indirect bilirubin levels.	**ATV:** 49% of children developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/ scleral icterus **IDV:** 10-25% of children developed increased total bilirubin levels; 15% had jaundice	Not associated with HBV or HCV	**Monitoring:** Assess bilirubin levels periodically, especially in first few months on regimen.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).

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

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, DM*	Thymidine analogue NRTIs (d4T, ddI, ZDV) Some PIs (IDV, LPV/r, perhaps less often ATV or FPV); unclear if class effect	**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 (2–4-fold greater than that for non-HIV-infected adults) *ARV-treated children:* Very rare in HIV-infected children	**Risk factors for Type 2 DM:** • Lipodystrophy, metabolic syndrome • Family history of DM • Overweight, obesity	**Prevention:** Lifestyle modification (see Management). Although uncertain, avoiding use of d4T, PI-containing regimens 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, smoking cessation). 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:* Suggests no current insulin resistance; recheck FPG in 6–12 months.

* 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; d4T = stavudine; ddI = didanosine; DM = diabetes mellitus; FPG = fasting plasma glucose; FPV = fosamprenavir; 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; ZDV = zidovudine

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (alone and in combination)	**Onset:** 1–20 months after starting therapy (median onset 4 months in one case series). **Presentation:** Usually insidious onset of a combination of signs and symptoms: generalized fatigue, weakness and myalgias, vague abdominal pain, sudden weight loss, unexplained nausea or vomiting, dyspnea, peripheral neuropathy. Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, and respiratory failure).	**Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L):** *Adults:* 15%–35% ≥6 months after initiation of NRTI *Children:* 29%–32% **Symptomatic severe hyperlactatemia (>5.0 mmol/L):** *Adults:* 0.2%–2.5% **Symptomatic lactic acidosis/hepatic steatosis:** Rare, but associated with a high fatality rate (33%–57%)	**Adult risk factors:** • Female gender • High BMI • Chronic HCV infection • African-American race/ethnicity • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (e.g., d4T, TDF, RBV, or tetracycline) • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly, pregnancy **Child risk factors:** Unknown	**Prevention:** Avoid d4T and ddI in combination. Monitor to recognize clinical manifestations of lactic acidosis early on 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*; 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)† 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.

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

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

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy (fat redistribution)—general information	See below	**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	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 prior to initiation of therapy	**Prevention:** Calorically appropriate, low-fat diet and exercise. **Monitoring:** Measure BMI.	Calorically appropriate, low-fat diet and exercise, especially strength training. There are insufficient data to allow the Panel to safely recommend the 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 (<15%) in patients not treated with d4T or ZDV	d4T and ZDV Obesity prior to ART	**Prevention:** Avoid use of d4T and ZDV. **Monitoring:** Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. There are insufficient data to allow the Panel to safely recommend the 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: ART = antiretroviral therapy; ARVs = antiretrovirals; BMI = body mass index; 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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ nephrolithiasis	IDV, ATV	**Onset:** Weeks to months after initiation of 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	Unknown	**Prevention:** Maintain adequate hydration. **Monitoring:** Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative medication.
Renal dysfunction	TDF	**Onset:** Variable; in adults, weeks to months after initiation of therapy **Presentation:** May include proteinuria, urinary phosphate wasting, glycosuria, Fanconi's syndrome, acute tubular necrosis, increased serum creatinine, hypokalemia, and hypophosphatemia	**Adults**: ~2% with increased serum creatinine; ~0.5% with severe renal complications **Children:** ~4% with hypophosphatemia; ~25% with severe proteinuria in one study (may be confounded by its use in children with advanced HIV infection)	Risk may be increased by advanced HIV infection, concurrent use of ddI or PIs (especially LPV/r), and preexisting renal dysfunction.	Consider urinalysis, serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months.	If no other cause than TDF use can explain nephrotoxicity, consider using alternative medication.
	IDV	**Presentation:** Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If no other cause than IDV use can explain nephrotoxicity, use 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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and osteoporosis	Combination antiretroviral therapy (cART), especially following initiation of cART, regardless of regimen. Specific agents of possible concern: TDF, d4T, or PIs	**Onset:** Any age; greatest risk in months after initiation of associated ARV. **Presentation:** Most commonly asymptomatic; fracture (rare). Osteoporosis diagnosis in children requires clinical evidence of bone fragility and cannot rely solely on measured low bone density.	**Low bone density:** 20% of children treated with cART had BMD *z* score <-1.5.	• Longer duration of HIV infection • Greater severity of HIV disease • Growth delay, pubertal delay • Low BMI • Lipodystrophy • Nonblack race • Smoking • 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*. Obtain DXA†.	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. *Later stages:* Consider surgical intervention.

* 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.

† Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6–12 months for children in early puberty who are initiating treatment with TDF. DXA should also be obtained in children with indications not uniquely related to HIV infection (e.g., cerebral palsy)[10].

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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Table 17k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
ARV toxic neuropathy*	d4T, ddI	**Onset:** Variable, weeks to months following NRTI initiation **Presentation:** Pain described as aching, burning, painful numbness pain distribution bilateral soles of feet, ascending to legs and fingertips; hyperalgesia (lowered pain threshold) allodynia (non-noxius stimuli cause pain) decreased or absent ankle reflexes	**Perinatal HIV infection:** *Prevalence:* 1.13% (2001 baseline PACTG 219C) *Incidence:* 0.9%; 0.23 per 100 person-years (2001–2006) 0.1% incidence with use of d4T+3TC+NVP over mean follow-up of 1.3 years **HIV-infected adults:** 31% taking d4T	**HIV-infected adults:** • Pre-existing neuropathy (diabetes, alcohol abuse, vitamin B12 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. • There are insufficient data to allow the Panel to safely recommend the use of any of the following modalities in children: tricyclic antidepressants, gabapentin, pregabalin, mexilitine, or lamotrigine.

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

Key to Acronyms: 3TC = lamivudine; ARV = antiretroviral; d4T = stavudine; ddI = didanosine; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine

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Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Skin Rash, SJS/EM/TEN, HSR. Page 1 of 3.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Skin rash	Any ARV can cause skin rash.	**Onset:** First few days to weeks after initiation of 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	• Rash with a sulfonamide is a risk factor for rash with NNRTIs and the PIs containing a sulfonamide moiety (FPV, APV, DRV, TPV). • Possible association of the HLA-DRB 101 allele with rash with NVP or EFV.	*When starting NVP or restarting after interruptions ≥7 days:* Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.* Avoid the use of corticosteroids during NVP dose escalation. • Assess patient for rash severity and presence of systemic signs and symptoms (see also HSR).	**Mild-to-moderate rash:** Prescribe antihistamine as needed; the ARV medication can be continued.* **Severe rash (accompanied by blisters, fever, involvement of the oral/anal mucous membranes, conjunctivitis, edema, arthralgias):** • Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.) • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. • 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 initiation of therapy. **Presentation:** Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.	**Adults:** >90% (7% discontinued ENF)	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—Skin Rash, SJS/EM/TEN, HSR. Page 2 of 3.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
SJS/ EM major/ TEN	NVP, EFV, ETR, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	**Onset:** First few days to weeks after initiating therapy. **Presentation:** Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bullae formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.	**Infrequent:** NVP (0.3%), EFV (0.1%), ETR (<0.1%) **Case reports:** FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	**Adults:** • Female gender. • Race/ethnicity (Black, Asian, Hispanic). **Children:** Unknown	• *When starting NVP or restarting after interruptions ≥7 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.* • Counsel families to report symptoms immediately.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, intravenous 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)	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 because of racial/ethnic distribution of HLA-B*5701 alleles.	• Screen for HLA-B*5701. ABC should not be prescribed if HLA-B*5701 screen is positive. The medical record should clearly indicate that the patient is ABC allergic. • Counsel families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms such as an intercurrent viral illness. • Treat symptoms as necessary. • Most symptoms resolve 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—Skin Rash, SJS/EM/TEN, HSR. Page 3 of 3.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	NVP	**Onset:** Most frequent the first few weeks after initiation 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/mm3 in women; >400 cells/mm^3 in men). • Female gender (risk is 3-fold higher in females than in males). **Children:** NVP hepatoxicitiy and hypersensitivity may be less common in prepubertal children than in adults.	• 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.* • 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 post-exposure 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.
	ENF	**Onset:** Any time during therapy. **Presentation:** Symptoms may include rash, fever, nausea, vomiting, rigors, hypertension, elevated hepatic transaminases.	<1%	Unknown.	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARVs. Rechallenge with ENF is not recommended.

* The prescribing information for 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 the risk of NVP resistance due to subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. NVP should be stopped if the rash is severe or is worsening or progressing.

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

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Antiretroviral Treatment Failure in Infants, Children, and Adolescents (Updated August 11, 2011)

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

Overview

Although many children can remain on stable antiretroviral therapy (ART) for several years[1-4], at some point reassessment of a therapeutic regimen will become necessary. The definitions, causes, assessment, and management of ARV treatment failure and specific issues to consider when changing a drug regimen are discussed in this section of the guidelines. Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria. Not all instances of treatment failure require an immediate change in ART; a careful assessment is required to evaluate the etiology of treatment failure and determine the appropriate management strategy.

The approach to treatment failure in children who have received more than one ARV regimen is often more complex than the approach in children receiving their first regimen. However, with the availability of an increasing number of ARV agents, including those directed at new viral targets, the goal of treatment regimens for all patients—whether on initial, second, or subsequent regimen—is complete virologic suppression, combined with the recovery or maintenance of immunologic parameters and improvement in baseline clinical condition (or maintenance of clinical condition if asymptomatic). (See Assessment of Patients with Antiretroviral Treatment Failure and Management of Medication Toxicity or Intolerance.) Decisions regarding changing ART should be individualized and should take into consideration the 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[5], 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 (e.g., atazanavir; see Appendix A). In addition, dosing recommendations for adolescents have not been established for a number of new ARV medications now used in adults. Guidance on dosing in 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 response to therapy or as a viral rebound after virologic suppression is achieved.

- **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 8–12 weeks of therapy, HIV RNA >200 copies/mL after 6 months of therapy, or repeated HIV RNA greater than the level of detection using the most sensitive assay after 12 months of therapy. Achieving an undetectable viral load may take longer in children with higher HIV RNA levels at initiation of therapy, especially in infants[6]. In adult studies, persistent viremia <200 copies/mL does not necessarily constitute virologic failure[7].
- **Viral rebound:** For children whose plasma viral load was previously suppressed to an undetectable level in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive polymerase chain reaction (PCR) assays. "Blips," defined as isolated episodes of viremia <1,000 copies/mL followed by return to viral suppression, are common and not generally reflective of virologic failure[8-9]. Repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound[10-11].

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 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. Absolute CD4 count values in children approach those of adults at about 5 years of age; consequently, changes in absolute count may be used in children ≥5 years of age.

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

Clinical Failure: 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 pa-

tients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. For example, development of a new OI in a patient who had severe immune suppression when recently initiating therapy may reflect persistent immune dysfunction despite adequate virologic response and not failure to achieve virologic suppression. Additionally, immune reconstitution inflammatory syndrome (IRIS) should be excluded as a possible cause of clinical illness before concluding that the clinical response to therapy is suboptimal. Clinical events occurring in the first several months after ART initiation should not necessarily be construed as ART failure. 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, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.
- **Growth failure.** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness.** Recurrence or persistence of AIDS-defining conditions or other serious infections.

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

Discordance between Viral, Immune, and Clinical Responses

In general, highly active combination antiretroviral therapy (HAART) that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of new or recurrent HIV-related illnesses. The inverse is also generally true: ineffective ART that fails to suppress viremia is commonly accompanied by concordant immunologic and clinical failure[12]. 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 ART may occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that ART failure has truly occurred.

Adequate Clinical and Immunologic Responses despite Incomplete Virologic Response: Some patients who are maintained on HAART may sustain immunologic and clinical benefit for up to 3 years despite persistently detectable viremia[13-22]. This observation is the rationale for continuing nonsuppressive ART for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practical. The risks and 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 the maintenance of a lower viral load or the selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation 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 nonprogressors" without therapy.

Poor Immunologic Response despite Virologic Suppression Regardless of Clinical Response: Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. The first considerations in cases of poor immunologic response despite virologic suppression

are to exclude laboratory error in CD4 or viral load measurements and to ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count over the first 5–6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection in Infants and Laboratory Monitoring of Pediatric HIV Infection). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary.

Additionally, 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 ART and may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression[3, 19, 23-27].

Certain ARV agents or combinations may be associated with a blunted CD4 response. Treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced[28] and this combination is not recommended as part of initial therapy. Dosing of didanosine should be adjusted when coadminstered with tenofovir. In adults, ARV regimens containing zidovudine may also impair rise in CD4 count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine[29]. Fortunately, this ARV drug-related suboptimal CD4 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 (TB), malnutrition, Sjogren's syndrome, sarcoidosis) are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in adults without HIV infection[30].

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 is not actually poor)
- Low pretreatment CD4 lymphocyte 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: hepatitis C coinfection, TB, malnutrition, Sjogren's syndrome, sarcoidosis

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 TB

- 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 ART. 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 ART is IRIS, which does not represent ART failure and does not generally require discontinuation of ART[31-32]. 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[33]. Such cases do not represent ART failure and, in these instances, children would not benefit from a change in ARV regimen. Before reaching a definitive conclusion of ART failure, the 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 TB, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jiroveci* pneumonia [PCP] or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason. Although such cases are rare, they may represent ART 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 (TB, malignancy)
- Malnutrition
- Clinical manifestations of previous organ damage: brain (strokes, vasculopathy), lungs (bronchiectasis)
- Clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Assessment of Patients with Virologic Failure of Antiretroviral Treatment

Panel's Recommendations
• Inadequate adherence is the most common cause of antiretroviral treatment (ART) failure. Assess adherence to therapy; address barriers and develop interventions to improve adherence **(AII)**.
• Assess medication intolerance **(AIII)**.
• Assess issues related to pharmacokinetics (PKs) because developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral (ARV) drug exposure that can result in ART failure **(AII)**.
• Perform ARV drug-resistance testing when virologic failure occurs; Perform testing while the 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*)**.

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

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

* At least two measurements (taken 1 week apart) should be performed to confirm initial laboratory results.

† Children with higher HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load[6]. Persistent viremia <200 copies/mL in adults does not necessarily constitute virologic failure[7].

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

Each patient with an incomplete response to therapy should be assessed to determine the cause of treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. The assessment of a child with suspicion of treatment failure should include evaluation of adherence to therapy; medication intolerance; issues related to PKs that could result in low drug levels or elevated, potentially toxic levels; and evaluation of suspected drug resistance. The main challenge to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with the subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the 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[34-35].

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 ART failure[36-41]. Although adherence should be addressed at each medical visit for all children receiving ART, suspicion of treatment failure warrants increased scrutiny. 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 the child and the family.

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 the child and 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 may 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 the child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting the child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and 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[42].

Pharmacokinetic Factors

Treatment failure can result from inadequate drug exposure as well as poor adherence[43]. Children consistently require higher weight-based dosing of ARV drugs compared with adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range[5]. Causes of subtherapeutic drug levels may include failure to increase dosing to accommodate for rapid growth of the child or impaired absorption because of gastrointestinal (GI) symptoms, such as vomiting or diarrhea. Because drug exposure may be enhanced or reduced by administering medications with food, the clinician should review the food/fasting requirements of the regimen with the patient and caregiver. Drug interactions can alter drug metabolism; 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 recent studies suggest that genetic polymorphisms may influence PKs and therapeutic response for a number of ARV medications[44-46]. In

Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure

Assessment	Method	Intervention
Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Get 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 2. Review pharmacy records • Assess timeliness of refills	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 coformulated under a third or fourth name. Explore opportunities for facility or home-based DOT.
	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 (pill boxes, reminders including alarms, integrated medication packaging for AM or PM dosing, others). 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 ART - 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.
Pharmacokinetics and Dosing	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific 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.
Resistance Testing	1. Perform genotypic and phenotypic resistance assays (see Antiretroviral Drug-Resistance Testing). 2. Perform tropism assay, as appropriate.	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).

some circumstances, therapeutic drug monitoring (TDM) 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 with inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs of the current regimen, it is unlikely that the child is currently taking these medications. The presence of mutations that confer resistance to one or more drugs in the regimen is indicative that the patient is adhering to the regimen but the regimen is failing to adequately suppress viral replication. ARV resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of discontinuing the regimen. In the absence of the selective pressure of ARV drugs, virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays. Resistance testing can be used to assess reasons for current virologic failure and to identify active ARV medications for future regimens. Other laboratory tests of drug resistance, such as tropism assays, may also be indicated if CCR5 inhibitors are being considered for treatment in the subsequent regimen.

Approach to the Management of Virologic Failure of Antiretroviral Treatment

Panel's Recommendations
• The causes of treatment failure, which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions, should be assessed and addressed **(AII)**.
• A consensus on how to treat immunologic failure or clinical failure in the setting of sustained virologic suppression does not exist **(AIII)**.
• 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*)**.

General

Once the causes of treatment failure have been identified and addressed, the child should be assessed to determine whether a change in the ARV regimen is necessary and advisable. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The immediacy of implementing a more effective treatment regimen depends on the immunologic status of the child, with the greatest urgency for patients with clinical disease progression or clinical failure. The likelihood of achieving and maintaining undetectable plasma viral load depends on the extent of drug resistance, the number and quality of available agents that are active against the child's virus, and the likelihood of adherence to the new regimen. If poor adherence was the cause of treatment failure and circumstances leading to poor adherence have not been adequately addressed, changing the ARV regimen may not be advisable.

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[18], the urgency of re-establishing virologic suppression depends on the clinical and immunologic status of a child. For example, for older children or adolescents with severe immunosuppression (e.g., 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[47-48].

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

When deciding whether to change a child's ARV 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[18]. However, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring mutations associated with resistance. 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[49], psychosocial stressors[50-51], health beliefs[52], and prior adherence to medication. (See Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents for more detail.) Importantly, adherence to ART may change rapidly and unexpectedly with a change in family circumstances or as the child moves through progressive developmental stages. Thus, a clinician may choose to target a new ARV regimen to start at a time when the child and 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 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 due to nonadherence, but it is important to exclude other factors such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be assured, then adherence to the current regimen should result in undetectable plasma levels. Resistance testing should take place while the 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 ART develops resistant virus and then stops therapy, sensitive virus will dominate in the absence of therapy. In this situation, resuming the prior therapy would fail to suppress the virus because the resistant virus would again emerge. An approach to identify resistance in this situation is to restart the prior medications while emphasizing adherence and repeat resistance testing in 4 weeks (unless undetectable plasma viral load has already been achieved). If plasma virus is undetectable by ultrasensitive assays, it is likely that the virus is susceptible to the current therapy.

Viral Resistance to Current Therapy

The goal in this situation is to start a new regimen in order to fully suppress and sustain plasma viral load below the limits of detection and prevent the emergence of virus with additional resistance muta-

tions. 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 (e.g., 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 assure 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 adult patients with treatment failure. Unfortunately, the lack of pediatric formulations and dosing information for many of these agents limit the number of options available for children. Thus, it remains difficult to identify a new, active regimen for many children with extensive prior therapy. (See The Use of Antiretroviral Agents Not Approved for Use in Children.)

If 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 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 <10,000–20,000 copies/mL may offer ongoing immunologic and clinical benefit[53-54]; pediatric studies suggest that children receiving cART with viral load <1,000–5,000 copies/mL may benefit less from changing therapy[48, 55]. Several cohort studies show a clinical benefit of remaining on ART whether this leads to a decrease in the viral load or not. 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 nonsuppressive protease inhibitor (PI)-containing regimens[56]. On the other hand, interrupting therapy completely may cause a rapid increase in viral load, a decrease in CD4 cell count that is frequently persistent, and an increased risk of clinical disease progression[50]. This approach should only be considered in special circumstances when there is a low risk that therapy interruption will quickly lead to severe immunosuppression (i.e., when CD4 values at the time of therapy interruption are high). The goal of continued treatment with an incompletely suppressive regimen is to select for resistant virus with reduced viral fitness that will cause slower disease progression while reducing the risk of drug toxicity and the development of new resistance mutations to multiple classes of drugs. The overall goal of these alternative strategies is to prevent clinical and immunological progression until additional active drugs are available that can be used to design a regimen that is expected to achieve undetectable plasma viral load[15-16, 18-21, 57-60]. This approach should be regarded as acceptable but not ideal; these patients should be followed more closely than patients with stable virologic status; and the potential to successfully initiate a fully suppressive ARV regimen should be reassessed at every opportunity.

When managing disease progression in a patient with advanced disease and extensive resistance, the patient's quality of life must be considered. The relative benefits (reduced viral fitness, continued clinical benefit despite resistance, etc.) and burdens of continuing a failing ARV regimen should be discussed. Decisions to continue, discontinue, or simplify ART should be made collaboratively with patients, fami-

lies, and clinicians and should be consistent with the patients'/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 would also be difficult, 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 nonsuppressive regimen or a simplified, NRTI-only nonsuppressive regimen that may provide some clinical and immunologic benefit while preserving future ARV choices (see Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance)[57, 61-62]. Treatment with nonsuppressive 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. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive ARV regimen should be reassessed at every opportunity.

Complete treatment interruption for the persistently nonadherent patient should prevent accumulation of additional drug resistance but does not offer potential clinical or immunologic benefit and has been associated with immunologic declines and poor clinical outcomes[63]. 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).

Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance

Panel's Recommendations
• Antiretroviral (ARV) regimens should be chosen based on treatment history and drug-resistance testing, including past and current resistance test results **(AI*)**.
• Ideally, the new regimen should include 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 (PK) and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist **(AIII)**.

General

After carefully reaching a decision that a change in therapy is needed, the clinician should attempt to identify at least two but preferably three fully active ARV agents on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence[64-68]. 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 be avoided because this approach is unlikely to achieve and sustain

an undetectable plasma viral load and frequently will result in additional drug resistance. A drug may be "new" to the patient but have diminished antiviral potency due to the presence of drug-resistance mutations that confer cross resistance within a drug class. In children who are changing therapy owing to occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher concentration levels within the central nervous system (CNS)[69-72].

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient in an age- and development-appropriate manner and with the patient's caregivers. The clinician must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate 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.

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

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

If a patient has substantial pre-existing resistance or if the initial regimen contained drugs from all three major classes (NRTI, NNRTI, and PI), the drug-resistance profile and management approach is likely to resemble that of a patient who has had multiple ARV regimen failures (see Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered). In this situation, a new regimen with only two fully active agents may be the best available option. Lopinavir/ritonavir-based regimens have shown durable ARV activity in ART-experienced children, including children with prior PI therapy[73-75]. Adult and adolescent studies of treatment-experienced patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), possibly coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced patients with multidrug-resistant virus, is associated with good virologic responses[76-79]. Appendix A: Pediatric Anti-

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

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

* ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI may 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.
† No current Food and Drug Administration (FDA)-approved pediatric indication for ETR, integrase inhibitor, and CCR5 antagonist.

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

retroviral 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 and integrase inhibitors. Maraviroc (CCR5 inhibitor) and raltegravir (integrase inhibitor) are approved for use in adolescents 16 years or older and can be considered for management of older adolescents with multidrug failure. Pediatric trials of these drugs are under way or in development.

Previously prescribed drugs discontinued because of poor tolerance or poor adherence may sometimes be reintroduced. Reintroduction of the drugs is particularly possible if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to pill formulation). Limited data in adults suggest that continuation of lamivudine can contribute to sup-

pression 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[80-82]. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children might be justified and is ideally done in the framework of a clinical trial (see The Use of Antiretroviral Agents Not Approved for Use in Children). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

The HIV entry inhibitor enfuvirtide (T-20) is approved for use in heavily treatment-experienced patients based on potent ARV activity in heavily treatment-experienced adults and has been approved for use in children ≥6 years of age[83-84]. Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children ≥6 years of age[85-86]. 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 as an option when designing a new regimen for children who have failed treatment with multiple classes of ARV medications; however, newer and better tolerated agents have largely supplanted use of enfuvirtide.

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[87-89] and in children[90-92]. PK studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs[93-94]. 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 1,000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks for ≥50% of patients. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series[95]; however, multidrug regimens should be used cautiously due to their complexity, poor tolerability, and unfavorable drug-drug interactions. TDM may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity due to the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may make use of dual-PI regimens unnecessary.

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

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

The creation of an effective and sustainable therapeutic regimen may not be possible with currently available agents due to lack of potency in the face of extensive drug resistance or the patient's inability to adhere to or tolerate cART.

In such cases, nonsuppressive regimens (or "holding regimens") are sometimes used pending availability of additional active drugs. 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. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive ART 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[61-62].

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[56].

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[96-98]. However, continued PI use, in the presence of resistance, may limit viral replication and be beneficial to some patients.

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

The Use of Antiretroviral Agents Not Approved for Use in Children

Panel's Recommendations
• Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age range 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)**.
• "Off-label" use of ARVs in children can be risky because, pending pediatric dosing recommendations, dosing often cannot be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Off-label 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)**.

It has long been practice for physicians, especially pediatricians, to prescribe medications in "off-label" situations, meaning for indications or populations that do not fall within the official, FDA-approved indication[99]. The relatively small market for pediatric 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 the number or severity of side effects with newer PIs and the ability to create simpler regimens using fixed-dose combination tablets or once-daily preparations. The incentive to use these drugs 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 the 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 incomplete viral suppression due to treatment with multiple nonsuppressive regimens. Cross resistance between fully approved ARVs within a class complicates finding an array 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 recent FDA approvals for adults of raltegravir and maraviroc (the first integrase inhibitor and CCR5 inhibitor, respectively) have provided new options for therapy to achieve virologic suppression in patients experiencing treatment failure with extensive ARV resistance.

However, 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 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 uniquely preclude use in children, but until an agent has been tested in children it cannot be considered to be free of such an effect. Additionally, adverse effects noted in adults may be of more substantial concern in the growing and developing child.

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[5]. 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[100].

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

Role of Therapeutic Drug Monitoring in Management of Treatment Failure

TDM is the use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in ART because[101-102]:

- Interpatient variability in ARV exposure (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 PK differences contribute to greater variability and a greater frequency of suboptimal ARV exposure in pediatric patients than in adults[5]. 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 frequently receive inadequate ARV doses[43].

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

For TDM to be useful, the relationship between ARV drug concentrations and anti-HIV effects must be clearly defined[103-105]. This association is strongest with PI and NNRTI drugs[106], but maintaining adequate NRTI serum concentrations has also been shown to be important for maximal anti-HIV activity[107]. The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents[105]. 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[108].

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 mini-

Table 21. Suggested Minimum Target Trough Concentrations*

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

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

mum target trough concentration should be based on results of resistance testing[109-111]. 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[106, 112-116]. The clinician should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

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

- Patients in whom clinical response is different from that expected;
- Treatment-experienced patients infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful;
- Patients 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
- Patients 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 the patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results[117-118];
- Single trough measurements within the target range do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third party reimbursement of costs associated with TDM.

Discontinuation or Interruption of Therapy

General

Discontinuation of ART 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 nonprescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy[50, 63]. 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; however, trials have demonstrated significantly higher morbidity and mortality for adults randomized to structured treatment interruptions (STI) compared with continuous HAART[119]. At this time, data about STI in infants, children, and adolescents are minimal[120]. Thus, STI should not be attempted in children or adults outside of

a clinical trial setting. The discussion below provides general guidance for the interruption of ART and the risks and benefits in specific situations.

Short-Term Therapy Interruption

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

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

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation[121-124]. As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in a slower rate of drug clearance. These polymorphisms may be more common among some racial/ethnic groups, such as African Americans and Hispanics[123-124]. To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other ARV drugs (i.e., NRTI backbone or PI) for a period of time[122]. However, the optimal interval between stopping an NNRTI and the other ARV drugs is not known. Detectable levels of NNRTIs may be present from <1 week to >3 weeks after discontinuation[124]. An alternative is to substitute a PI for up to 4 weeks prior to the interruption of all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective strategy. Information in children is not available and, because the PKs of these agents are different in children, the recommendations for adults may not be applicable[125-127].

An additional consideration is reintroduction of nevirapine. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing cytochrome P450 3A4 (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[125]. 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

Long-term STIs have been proposed to reduce toxicities and costs associated with long-term ART. STIs have also been proposed in patients who have limited treatment options to allow their strains of HIV to revert to wild-type virus, which may be more susceptible to treatment. At this time, only minimal information about STI in children is available. In 1 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[128]. However, new drug-resistance mutations were detected in 3 of 14 children in the STI study. In another trial, 109 children with virologic suppression on cART were randomized to continuous therapy (CT) ver-

sus treatment interruption with CD4-guided reinitiation 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 ART compared with children in the CT arm[129]. 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[129].

Recently, the results of two large, randomized clinical trials in adults have demonstrated inferior responses when CD4 cell count was used as an indication to stop and start therapy. The Strategies for Management of Antiretroviral Therapy stopped ART when the CD4 cell count was >350 cells/mm^3 and reintroduced therapy when the count was <250 cells/mm^3. In comparison to the group receiving continuous ART, the STI group had an increased risk of disease progression and death[119]. Similarly, in the Trivican trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior[130]. However, in studies in adults using a CD4 count <350 cells/mm^3 as a trigger to restart therapy, no significant difference in serious disease progression or death was seen[131–132]. A large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy[133]. Several additional trials are currently ongoing in adults.

Many questions remain about STI in children and adolescents. In the United States and other developed countries, the majority of HIV-infected children began ART during infancy[134–135]. Many of these children have had controlled viral replication for many years and are growing and developing normally. It is unclear if these children could discontinue therapy at some point and reinitiate treatment based on CD4 cell decline. The ongoing CHER study includes plans to assess outcomes of eligible children undergoing STI[136]. Currently, there are insufficient data to support use of STI in clinical care, and STI should not be attempted outside of a clinical trial setting.

Often raised is the additional scenario of the patient who has limited treatment options and who, despite aggressive ART, cannot reach an undetectable viral load. In these cases, interruption of therapy is generally not recommended because, despite detectable viral replication, immunologic benefit has been well documented[16-17, 20, 22].

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

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Antiretroviral Drug-Resistance Testing (Updated August 11, 2011)

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 for treatment failure **(AI*)**.
• Resistance testing in the setting of virological failure should be obtained while the patient is still on the failing regimen or within 4 weeks of discontinuing the regimen **(AII*)**.
• 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, especially if the ARV agent shares cross resistance with drugs previously used. In addition, current resistance assays are not sensitive enough to fully exclude the presence of resistant virus. Thus, previously used 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 a pediatric patient **(AI*)**.

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 (HIV RNA <40–80 copies/mL). Unfortunately, mutations in HIV RNA readily arise during viral replication because HIV reverse transcriptase (RT) is a highly error-prone enzyme. Consequently, ongoing replication in the presence of 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 employed to detect virus with tropism that will (CCRR5 tropism) or will not (CXCR4 or mixed tropism) be blocked by CCR5 antagonists. Both genotypic assays and phenotypic assays are used to detect the presence of virus that is resistant to inhibitors of the HIV RT, integrase, or protease (PR). Clinical experience with testing for viral resistance to other agents is more limited, but genetic mutations associated with resistance to integrase strand transfer inhibitors (INSTIs) have been identified, and a commercial phenotypic assay is available for evaluation of resistance to the fusion inhibitor enfuvirtide. Experience 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] is also limited.

Genotypic Assays

Genotypic assays for resistance to RT, PR, and INSTIs are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and integrase coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance-associated mutations in plasma samples containing approximately 1,000 copies/mL or more of HIV RNA and results are generally available within 1–2 weeks of sample collection[2]. Interpretation of test results requires knowledge of the mutations selected by different 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]. Other mutations have little direct effect on resistance but arise during HIV evolution to high-level resistance or improve the replication of virus-bearing mutations that confer high-level resistance to an ARV agent.

The International Antiviral Society-USA (IAS-USA), the Los Alamos HIV Drug Resistance Database, and the Stanford University HIV Drug Resistance Database maintain lists of significant resistance-associated mutations relevant to currently available ARV drugs (see http://www.iasusa.org/resistance_mutations, http://hiv-web.lanl.gov, or http://hivdb.stanford.edu). A variety of online tools that take into account the ability of some mutations selected by one drug to cause partial or full cross resistance with other drugs are now available to assist the provider in interpreting genotypic test results. Although the response to 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, integrase, PT, or other HIV gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a laboratory strain of HIV. Replication of this recombinant virus at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration, or IC50) is calculated, and the ratio of the IC50 of test and reference viruses is reported as the fold increase in IC50 (i.e., fold resistance change). Automated, recombinant phenotypic assays that can produce results in 2–3 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 and PI resistance only, matches the pattern of mutations obtained from the patient sample with a large database of samples for which both genotype and phenotype are known. Thus, the sample is assigned a predicted phenotype susceptibility (or "virtual phenotype") based on the data from specimens matching the patient's genotype. The primary limitations of this approach are that its predictive power depends upon the sensitivity of the

genotypic methods used and the number of matched phenotypic and genotypic assays available for data analysis, which may be limited for newer drugs.

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, then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses in the majority of untreated individuals, including infants and children infected by mother-to-child transmission (MTCT) of HIV, are initially CCR5 tropic. However, a shift in coreceptor tropism often occurs over time, from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (dual- or mixed-tropic; D/M-tropic). 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-cell counts[11].

Resistance to CCR5 antagonists is currently detected using the 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. 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. A newer version of the Trofile assay with improved sensitivity able to detect CXCR4- or D/M-tropic virus representing as little as 0.3% of the plasma virus is now available[12-13]. A genotypic assay to detect mutations associated with CXCR4- or D/M-tropic virus (Trofile-DNA) is also available. Although experience with these genotypic assays is somewhat limited, evidence that they may be useful substitutes for phenotypic tropism assays does exist[14]. Any indication of CXCR4 tropism is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor use assays should be performed before the use of a CCR5 inhibitor and may be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc. Because genotypic tropism assays can be performed on peripheral blood DNA, they 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%–20% of the circulating virus population may not be detected by any of the currently available commercial assays[15]. 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.

Although drug resistance may be detected in infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4–6 weeks after ARV drugs are stopped[16-18]. As a result, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued. The absence of de-

tectable 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 Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

Use of Resistance Assays in Determining Initial Treatment

MTCT 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 in infected infants[25] for months after birth and impair the response to ART[26]. Consequently, ARV drug-resistance testing is recommended prior to initiation of therapy in all treatment-naive children. 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 antiretroviral therapy (cART) 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 Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

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Conclusion

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 Disease 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 Web site[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)

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:
ABC is not approved for infants <3 months of age.

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 cell count, may consider using once-daily ABC dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see Pediatric Use).

Scored 300-mg tablet (body 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 to <30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (≥16 years of age)/adult dose:
300 mg twice daily or 600 mg once daily.

Trizivir
Adolescent (body weight ≥40 kg)/adult dose:
One tablet twice daily.

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

Selected Adverse Events

- Hypersensitivity reaction (HSR) 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 the risk of serious, potentially fatal HSR. Do not rechallenge.

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, patients on dialysis, or patients with impaired hepatic function.

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

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome 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 (NNRTIs).
- 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 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 by signs or symptoms in two or more of the following groups: (1) fever; (2) constitutional, including malaise, fatigue, or achiness; (3) gastrointestinal (GI), including nausea, vomiting, diarrhea, or abdominal pain; or (4) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests (LFTs), elevated creatine phosphokinase (CPK), 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 rechallenge. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.
- *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides (TGs), 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 children with HIV infection as one of the drugs for part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral (ARV) therapy. 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 <12 years of age 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 ages 2–13 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_{0-24} for both drugs and improved acceptability in the once-daily dosing arm[15-16]. However, trough concentrations were lower in younger children (ages 2–6 years) receiving the once-daily regimen[16]. The PENTA-15 crossover trial studied 18 children ages 3–36 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_{0-24} 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 ages 3–6 years (median age 7.6 years) in Uganda who were stable on twice-daily abacavir also showed equivalent AUC_{0-24} and good clinical outcome (disease stage and 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		US		US	
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

* 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 combination antiretroviral therapy (cART) 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) could be considered.

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Didanosine (ddI, Videx)

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 (2 weeks to <3 months of age):
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 [PK] data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 of body surface area every 12 hours.)

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

Pediatric dose of oral solution (>8 months of age):
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 (ages 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 3–21 years of age, 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)
- Potential association with noncirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddI, it is generally recommended to administer ddI on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer ddI without regard to timing of meals (see Pediatric Use).
- ddI oral solution contains antacids that may interfere with the absorption of other medications.
- Shake ddI oral solution well before use. Keep refrigerated; admixture is stable for 30 days.

Metabolism

- Renal excretion 50%.

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:
There is no data on this combination in children or adolescents <18 years of age, 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

- **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 (CrCl).

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

- *Absorption:* The presence of antacids in the didanosine suspension has the potential to decrease the absorption of a number of medications if given at the same time as didanosine. 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 coadministered with tenofovir and this combination should be avoided if possible.
- *Renal elimination:* Drugs that decrease renal function could decrease clearance of didanosine.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* The 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 didanosine is used in combination with tenofovir), 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:* Noncirrhotic portal hypertension, 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[4-5].

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 90–150 mg per meter^2 body surface area per dose twice daily. Doses higher than 180 mg per meter^2 body surface area twice daily are associated with increased toxicity[6]. In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg per meter^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with a predicted 88% of patients at a dose of 120 mg per meter^2 body surface area twice daily[7], which is the currently recommended dose for children from 8 months to 3 years of age.

For infants from 2 weeks to 8 months of age, the FDA recommends 100 mg per meter^2 body surface area per dose twice daily, increasing to 120 mg per meter^2 body surface area per dose twice daily at age 8 months. However, two small studies suggest that higher areas under the curve (AUCs) are seen in infants <6 weeks of age and that a dose of 100 mg per meter^2 body surface area per day (either as 50 mg per meter^2 body surface area per dose twice daily or 100 mg per meter^2 body surface area once daily) in infants <6 weeks of age achieves AUCs consistent with those of higher doses in older children[8-9]. Therefore, because these PK differences in younger infants (2 weeks to 3 months of age) compared with older children raise concern for increased toxicity in that age group, the Panel recommends a dose of 50 mg per meter^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 from 4 to 10 years of age, EC didanosine (Videx EC) administered as a single dose of 240 mg per meter^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 children with HIV infection, didanosine oral solution at a dose of 180 mg per meter^2 body surface area once daily was compared with 90 mg per meter^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group[10]. In PACTG 1021 long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution and EC beadlet capsules) was reported in 37 treatment-naive children 3 to 21 years of age[11]. The didanosine dose used in that study was 240 mg/meter^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 that included didanosine at a dose of 200–240 mg per meter^2 body surface area in 36 children 3 to 11 years of age demonstrated safety and efficacy with up to 96 weeks of follow-up data[12]. In 53 children with ad-

vanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg per meter^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy[13].

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and may decrease medication 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 was similar; however, absorption of didanosine administered with food was slower and more prolonged[14]. To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults have suggested 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[12].

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Emtricitabine (FTC, Emtriva)

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

Formulations

Pediatric oral solution: 10 mg/mL

Capsules: 200 mg

Combination tablets:
- *With tenofovir (TDF):* FTC 200 mg + TDF 300 mg (Truvada)
- *With TDF and efavirenz (EFV):* FTC 200 mg + TDF 300 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose (0–3 months of age):
Oral solution: 3 mg/kg once daily.

Pediatric dose (≥3 months–17 years of age):
Oral solution:
6 mg/kg (maximum dose 240 mg) once daily.

Capsules (for children who weigh >33 kg):
200 mg once daily.

Adolescent (≥18 years of age)/adult dose:
Oral solution: 240 mg (24 mL) once daily.
Capsules: 200 mg once daily.

Combination Tablets
Truvada (FTC + TDF)
Adult dose: 1 tablet once daily.

Atripla (FTC + TDF + EFV)
Adult dose: 1 tablet once daily.

See efavirenz section for pregnancy warning.

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, predominantly observed in nonwhite patients.

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 temperatures 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 mL/min or in patients requiring dialysis.
  - Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring dialysis.

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

- *Other 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.

Major Toxicities:

- *More common:* Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children).
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in HIV/HBV-coinfected patients 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 combination antiretroviral therapy (cART).

A single-dose PK study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children 2–17 years of age[1]. Emtricitabine was found to be well absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg emtricitabine once-daily dose were approximately equivalent to concentrations 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 3 months to 21 years of age[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 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 <3 months of age, 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 >3 months of age 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. No safety issues were identified in this short PKs study; however, extensive safety data are lacking in this age group.

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Lamivudine (3TC/Epivir)

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

Formulations

Oral Solution: 10 mg/mL (Epivir); 5 mg/mL (Epivir HBV*)

Tablets: 150 mg (scored) and 300 mg (Epivir); 100 mg (Epivir HBV*)

Combination Tablets:

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

** Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The formulation and dosing of 3TC in Epivir HBV was maximized for the 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

Epivir (oral solution and tablets)

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 (maximum dose 150 mg) twice daily.

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

Weight (kg)	AM dose	PM dose	Total Daily Dose (mg)
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <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:
4 mg/kg (up to 150 mg) twice daily.
Body weight ≥50 kg:
150 mg twice daily or 300 mg once 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 (body weight ≥30 kg)/adult dose:
1 tablet twice daily.

Trizivir
Adolescent (body weight >40 kg)/adult dose:
1 tablet twice daily.

Epzicom
Adolescent (age >16 years and body 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 from birth onward, and it is a common component of most nucleoside backbone regimens.

Lamivudine alone and in combination with other antiretroviral (ARV) drugs has been studied in HIV-infected children, 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]. Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life[11]. Recently, weight-band dosing recommendations for lamivudine have been developed[19-20].

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. The pharmacokinetics (PKs) of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children 2 to 13 years of age in the PENTA-13 trial[2] and in children 3 to 36 months of age in the PENTA 15 trial[21]. Both trials were

crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. Area under the curve $(AUC)_{0-24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children 3 to 12 years of age (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC_{0-24} and good clinical outcome (disease stage and CD4 cell count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years[22]. 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 (see table below). There are no clinical trials of combination therapy with once-daily dosing of lamivudine in children. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine in clinically stable patients with 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 (ART) in children.

Table: Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine*

Study/(reference)	PENTA 15[21]		PENTA 13[2]		Arrow[22]	
Location	Europe		Europe		Uganda	
N	17		14		35	
Age (years)	2		5		7	
Sex (% male)	56%		43%		42%	
Race (% black or African American)	78%		Not Reported		100%	
Body weight (kg)	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_{0-24} (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 unmetabolized 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 age 16 years and older who weigh 50 kg or more[23, 24].

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Stavudine (d4T, Zerit)

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

Formulations

Oral Solution: 1 mg/mL

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

Generic: 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 (14 days and body weight <30 kg):
1 mg/kg twice daily.

Adolescent (body weight ≥30 kg)/adult dose:
30 to <60 kg: 30 mg twice daily.
≥60 kg: 40 mg twice daily*.

* The World Health Organization (WHO) recommends 30 mg twice daily regardless of body weight in adults (see Pediatric Use).

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])
- 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. Toxicities are more often reported in adults and include se-

rious, 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 (HCV) coinfected patients receiving combination antiretroviral therapy (cART), interferon, and ribavirin.

Major Toxicities:

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

Resistance: The International 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 antiretrovirals (ARVs) demonstrate that stavudine appears safe and is associated with clinical and virologic response[1-7]. In resource-limited countries, stavudine is frequently a component of initial cART 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 count and complete viral suppression in 50%–80% of treatment-naive children[8-11]. 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 those patients requiring cotrimoxazole prophylaxis[12].

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving cART[13-14]. 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[14]. Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults[2, 15]. In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children[14]. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly stavudine, in adults and children[16-19]. 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[20]. Among 90 children receiving stavudine, lamivudine, and either nevirapine or efavirenz, 65% developed lipodystrophy at 33 months[21].

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, including stavudine, alone or in combination[22-24]. 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[25]. (For additional information on lactic acidosis see Table 17g 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 (PBMCs), and other tissues[22, 26-28]. In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219 C), possible mitochondrial dysfunction was associated with NRTI use, especially in those children receiving stavudine and/or lamivudine[29].

WHO recommends that stavudine be phased out of use because of serious, irreversible side effects and that a maximum stavudine dose of 30 mg be used instead of the FDA-recommended 40 mg in adults weighing 60 kg or more. Several studies have compared the efficacy and toxicity of the two doses: HIV suppression was found to be similar in adult patients treated in South Africa with either the 30-mg or 40-mg dose[30]; the incidence of peripheral neuropathy in adults treated in South Africa was significantly lower in the 30-mg group than in the 40-mg group, but the overall incidence was considered to be unacceptably high[31]. To reduce the risk of or to manage toxicity, some Panel members support switching to another agent if available rather than lowering the maximum dose. This recommendation is based on the availability of alternative ARV agents in the United States and on concerns for underdosing some patients with stavudine. However, other Panel members prefer using the 30-mg maximum dose of stavudine when there are limited alternatives.

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Tenofovir Disoproxil Fumarate (TDF, Viread)

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

Formulations

Tablet: 300 mg

Combination tablets:

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

Dosing Recommendations

Neonate/infant dose:
TDF is not approved for use in neonates/infants.

Pediatric dose*:
TDF is not approved for use in children <12 years of age. Investigational doses of 210 mg/m^2 body surface area (range 175 to 300 mg/m^2) have been used once daily in children <12 years of age.

Adolescent (≥12 years of age and body weight >35 kg) dose*:
300 mg once daily
*See Pediatric Use for concerns about decreased bone mineral density (BMD), especially in prepubertal patients and those in early puberty (Tanner Stages 1 and 2).

Combination Tablets
Adult dose: 300 mg once daily.

Truvada (TDF + FTC)
Adult dose: 1 tablet once daily.

Atripla (TDF + FTC + EFV)
Adult dose: 1 tablet once daily.

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).

Selected Adverse Events

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

Special Instructions

- 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.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV can occur when TDF is discontinued; therefore, monitor hepatic function for several months after therapy with TDF is stopped.

Metabolism

- Renal excretion.
- **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 (CrCl).
  - Atripla (fixed-dose combination) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
  - Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.

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

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

Major Toxicities:

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in 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 (BUN), 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 ≥12 years of age and ≥35 kg body weight when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (Tanner Stages 1 and 2) appear to be at higher risk than children with more advanced development (Tanner Stage ≥3)[1-3]. In a Phase I/II National Institutes of Health (NIH) study of an investigational 75-mg formulation of tenofovir involving 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[4]. 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[4-5]. In a second study of 6 patients who received the commercially available 300-mg formulation of tenofovir, 2 prepubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her antiretroviral therapy (ART) regimen with subsequent recovery of BMD[6]. Loss of BMD at 48 weeks was associated with higher drug exposure (area under the curve [AUC])[5]. Factors contributing to higher drug exposure in these studies included receiving ritonavir,

which increases tenofovir concentrations, and receiving higher doses of tenofovir. Although the median initial dose in the Phase I/II studies was 208 mg/m^2 (= 7.1 mg/kg), the administered dose varied from 161 to 256 mg/m^2 (3.7–10 mg/kg)[1]. However, in this heavily pretreated cohort, the group with the best virologic response had statistically significantly higher AUC, suggesting that in salvage therapy tenofovir may have a relatively small therapeutic window, especially in children in Tanner Stages 1 and 2. Plasma HIV RNA concentrations ($\log_{10}$ copies/mL) decreased from a median pretreatment concentration of 5.4 $\log_{10}$ copies/mL to 4.21 $\log_{10}$ copies/mL after 48 weeks of therapy[5]. HIV RNA was <400 copies/mL in 6 of 16 participants (37.5%) and <50 copies/mL in 4 of 16 participants (25%) at 48 weeks. In contrast, no effect of tenofovir on BMD was found in another study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz[7]. This study enrolled children who were older, not receiving ritonavir, and receiving lower doses of tenofovir with potentially lower drug exposures[7-9]. All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen. Lipid profiles improved significantly after the switch from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz[8].

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in persons with higher tenofovir trough plasma concentrations[10]. 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[11]. Possible tenofovir-associated nephrotoxicity manifest as Fanconi syndrome, reduced 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[12]. Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine[13]. 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[14]. 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[15]. Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovir-containing ARV 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[16]. However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years[17].

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, 18]. Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure[1]. 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[19].

Virologic success is related to prior treatment experience when evaluating the response to a tenofovir-containing regimen. In the CHIPS cohort 115 patients had outcome data available[11]. Viral load decreased

to <50 copies/mL at 12 months in 38% of patients starting tenofovir for the first time, in 50% of patients on first-line therapy, in 39% of patients on second-line therapy, and in 13% of patients on third-line or subsequent therapy[11]. The CHIPS 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 the NIH study[5], lower single-dose and steady-state AUC were associated with inferior virologic outcome. The Italian study[8], which used a lower dose than the NIH study (and reported less bone toxicity), studied only subjects who were well controlled on current ART.

In March 2010, the FDA approved the use of tenofovir in adolescents ≥12 years of age and weighing ≥35 kg based upon data from Gilead Study 321, a randomized, placebo-controlled trial of tenofovir or placebo plus an optimized background regimen in 87 treatment-experienced adolescents 12 to <18 years of age in Brazil and Panama[20-21]. No difference in viral load response was seen between the 2 groups. Subgroup analyses suggest this lack of response may have been due to imbalances in viral susceptibility to the optimized background regimens between the 2 groups. Importantly, impaired bone accrual was seen in the tenofovir group, manifest by declining BMD *z* scores over 48 and 96 weeks. In addition, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with only 1 of 33 participants (3%) in the placebo arm[20-21] (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf). Limited PK data were reported from 8 participants and suggested that tenofovir exposures were higher than those seen in the NIH study, but no data on correlation of tenofovir exposure with BMD loss were provided.

Although some studies of tenofovir use in children have not identified decline in BMD[22-23], given the potential for BMD loss, some experts recommend obtaining a DXA prior to the initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner Stages 1 and 2). However, in view of the potential cost and difficulty in obtaining pediatric DXA in some settings, other experts avoid using tenofovir in prepubertal patients and those in early puberty, especially for initial therapy. Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group. There is still an urgent need for more research to develop appropriate pediatric formulations and to identify the safest uses of tenofovir in children and adolescents.

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Zidovudine (ZDV, AZT, Retrovir)

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

Formulations

Capsules: 100 mg

Tablets: 300 mg

Syrup: 10 mg/mL

Concentrate for injection or intravenous infusion: 10 mg/mL

Generic: ZDV capsules, tablets, and solution are approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Combination Tablets:

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

Dosing Recommendations

Dose for infant <35 weeks gestation for prevention of transmission or treatment (standard neonate dose may be excessive in premature infants):
1.5 mg/kg of body weight (intravenous) or
2 mg/kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age).

(See Perinatal Guidelines for additional information.)

Neonate/infant dose (<6 weeks of age) for prevention of transmission or treatment:
Oral: 2 mg/kg of body weight every 6 hours.

Intravenous: 1.5 mg/kg of body weight every 6 hours.
(See Perinatal Guidelines for additional information.)

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.

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.

Metabolism

- Metabolized to AZT glucuronide (GAZT), which is renally excreted.

Weight-based dosing:

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

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

Adolescent (≥18 years of age)/adult dose:
300 mg twice daily.

Combivir (ZDV + 3TC)
Adolescent (weight ≥30 kg)/adult dose:
1 tablet twice daily.

Trizivir (ZDV + 3TC + ABC)
Adolescent (weight ≥40 kg)/adult dose:
1 tablet twice daily.

- **Dosing of ZDV in patients with renal impairment:** Dosage adjustment is required in renal insufficiency.
- **Dosing of ZDV 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. 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 combination antiretroviral therapy (cART)[4-19]. Pediatric experience with zidovudine both for treatment of HIV and for the prevention of mother-to-child transmission (PMTCT) is extensive.

Perinatal trial PACTG 076 established that a zidovudine prophylactic regimen given during pregnancy, labor and delivery, and to the newborn reduced the risk of perinatal transmission of HIV by nearly 70%[20]. (Consult 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.)

Overall, zidovudine pharmacokinetics (PKs) in pediatric patients >3 months of age are similar to those in adult patients. 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[21]. 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[22].

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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 (TMC 278, Edurant)

Efavirenz (EFV, Sustiva)

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

Formulations

Capsules: 50 mg and 200 mg

Tablets: 600 mg

Combination Tablets:

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

Dosing Recommendations

Neonate/infant dose:
EFV is not approved for use in neonates/infants.

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

Children ≥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 of 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.

Atripla (EFV + FTC + TDF)
Atripla should not be used in pediatric patients

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
- Teratogenic
- Lipohypertrophy although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors (PIs)

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 adolescent women of childbearing age because of the risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).
- CYP3A4 and CYP2B6 substrate.
- **Dosing of EFV in patients with hepatic im-**

<40 kg where the EFV dose would be excessive.
Adult dose: One tablet once daily.

EFV in combination with other antiretroviral (ARV) drugs:
Dosage adjustment or the addition of ritonavir (RTV) may be necessary when EFV is used in combination with atazanavir (ATV), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).

pairment: 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 Pediatric Use 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 with efavirenz.
- Before efavirenz is administrated, the patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. 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 (positive evidence of human fetal risk). Efavirenz use in the first trimester of pregnancy should be avoided. Women of childbearing age should undergo pregnancy testing and be counseled about the risks associated with fetal exposure to efavirenz and the need to avoid pregnancy before initiating and during efavirenz therapy.

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 combination antiretroviral therapy (cART) in children 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 (TB)-coinfected children younger than age 3 years. In addition, efavirenz should be used with caution in adolescent women of childbearing age because of the 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, 8-10]. Therefore , some experts recommend TDM 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 1 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 ages 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[11]. TDM 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[12]. 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[13]. 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. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations[6, 14-17]. 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[12] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL[3]. CNS side effects may be harder to detect in children because of the difficulty assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients. TDM can be considered for children with mild or moderate toxicity possibly at-

tributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In that situation, it is reasonable for the clinician to use TDM to determine if the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range[18-19]. 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 be used with caution in adolescent women of childbearing age because of the risk of teratogenicity[20]. 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[21]. Many clinicians choose alternative drugs for use in sexually active adolescent females because of the potential for erratic use of contraception and the high risk of unintended pregnancy.

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Etravirine (ETR, Intelence, TMC 125)

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

Formulations

Tablets: 100 mg and 200 mg

Dosing Recommendations

Neonate/infant dose:
ETR is not approved for use in neonates/infants.

Pediatric (6-11 years of age) dose:
ETR is not approved for use in children. Investigational dose currently in Phase II trial is 5.2 mg/kg (maximum 200 mg) twice daily in children ≥6 years of age.

Adolescent (12-17 years of age) dose:
ETR is not approved for this age group. Preliminary data from the Phase II trial (5.2 mg/kg, maximum 200 mg, twice daily–see Pediatric Use section) showed lower exposure than adults.

Adult dose (antiretroviral [ARV]-experienced patients):
200 mg twice daily following a meal.

Selected Adverse Events

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

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.
- ETR tablets are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in a small amount of water. Instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times, and each time the rinse water should be swallowed completely to ensure that the entire dose is consumed.
- **Dosing of ETR in patients with hepatic impairment:** No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- **Dosing of ETR in patients with renal impairment:** Dose adjustment is not required in patients with renal impairment.

Metabolism

- Metabolism by cytochrome P450: inducer of cytochrome P450 3A4 (CYP3A4) and inhibitor of CYP2C9 and CYP2C19. Substrate for CYP3A4, 2C9, and 2C19. Also inhibitor of p-glycoprotein (Pgp).
- Multiple drug interactions (see below).

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

- *Metabolism:* Etravirine is an inducer of CYP3A4; an inhibitor of CYP2C9 and CYP2C19; and a substrate for 3A4, 2C9, and 2C19. Etravirine is also an inhibitor of Pgp.
- Etravirine is associated with multiple drug interactions.
- Before etravirine is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with etravirine.
- Etravirine should not be coadministered with the following ARVs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors (PIs), nevirapine, or efavirenz.

Major Toxicities:

- *More common:* Nausea, diarrhea, mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of non-nucleoside reverse transcriptase inhibitor (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:* Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, 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 (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia) develop. 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 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/ETR.html).

Pediatric Use: Etravirine is not Food and Drug Administration (FDA) approved for use in children and the pharmacokinetics (PKs), safety, and efficacy of etravirine in pediatric patients have not been established. Pediatric experience with etravirine is limited and pediatric trials are under way.

A Phase I dose-finding study involving 21 children, 6–17 years of age, 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 an investigational 25-mg formulation and the available 100-mg formulation[1]. Etravirine therapy was added for 1 week and PK sampling and analysis were performed. Given the concern for underdosing in children and the lack of a safety signal in this study, the higher 5.2-mg/kg twice-daily dose is currently being studied in a Phase II trial[2] in pediatric patients.

The week 24 population PK data from this Phase II trial (101 treatment-experienced children 6-17 years of age) revealed lower etravirine exposures in adolescents (12-17 years of age) compared to 6-11 year old children and to adults (see table below).

	Median AUC_{12} (ng*h/mL)	Median C_{0h} (ng/mL)
Children 6-11 years of age (N=41)	5,289	342
Adolescents 12 to 17 years of age (N=60)	3,775	236
Adults (DUET study)	4,380	299

Of note, 93% of the adolescents were receiving the adult dose of etravirine (200 mg twice a day).

Despite insufficient data to recommend a pediatric dose, etravirine is being used in the salvage therapy setting in pediatrics. A report describing 12 heavily treatment-experienced, perinatally infected children who were monitored as part of the French Expanded Access Program (200 mg twice daily, range 2.8–5.3 mg/kg twice daily; median age 15 years, range 12–17 years) demonstrated good tolerability and virologic responses[3]. Similar results were seen in a study of 23 patients (median age 14.2 years) in Spain[4]. Median follow-up was 1 year in both studies.

An analysis of genotypic and phenotypic HIV resistance profiles in 35 children from a Ugandan clinic with clinical failure of a first-line regimen containing an NNRTI other than etravirine demonstrated reduced etravirine susceptibility (fold-change >2.9) in 35% of samples.

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Nevirapine (NVP, Viramune)

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:

Neonate/infant dose (age ≤14 days):

See Perinatal Guidelines for information on use of NVP for prophylaxis of mother-to-child transmission (MTCT) of HIV. Treatment dose is not defined for infants age ≤14 days.

Pediatric dose (age ≥15 days):

(See note below about initiation of therapy.)

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

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

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

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P (CYP) 450 metabolizing enzymes, which results in increased clearance of the drug. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/adult dose:

200 mg twice daily.

Note: Initiate therapy with 200 mg given once daily

Selected Adverse Events

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

Special Instructions

- NVP 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 NVP dose until rash resolves (see Major Toxicities).
- If NVP dosing is interrupted for more than 7 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests (LFTs), is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of LFTs 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 LFTs performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions (HSRs).
- Shake NVP suspension well and store at room temperature.

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

400 mg extended release 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 nevirapine 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.

Metabolism

- Metabolized by CYP450 (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:* Nevirapine induces hepatic CYP450 including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2–4 weeks, with a 1.5–2-fold increase in clearance. There is potential for multiple drug interactions with nevirapine. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than they do in efavirenz. Altered side 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 nevirapine is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with nevirapine. Nevirapine should not be coadministered with atazanavir (with or without ritonavir).

Major Toxicities (Note that these toxicities are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis):

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including SJS and toxic epidermal necrolysis [TEN]), 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 nevirapine dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against the patient's overall ability to tolerate the regimen and the current antiviral response.

- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of HSR. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). HSRs 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 HSRs.

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/NVP.html).

Pediatric Use: Nevirapine is Food and Drug Administration (FDA) approved for use in children from infancy onward and remains a mainstay of therapy, especially in resource-limited settings. Nevirapine has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI)[2-10].

In infants and children previously exposed to single-dose nevirapine for prevention of mother-to-child transmission (PMTCT), nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-based ART to control virus load. In a small, nonrandomized study in Botswana, 6-month virologic and immunologic responses were compared between 15 infants who were exposed to single-dose nevirapine and 15 who were not exposed who initiated nevirapine-based ART at a mean age of 8 months (range 2–33 months) in follow-up from a PMTCT study[11]. Only 34% of the infants with a history of nevirapine exposure had an undetectable viral load (<400 copies/mL) compared with 91% of the unexposed cohort. CD4 percentage was also significantly lower in the exposed group (23%) compared with the unexposed group (31%). In contrast, in a study in Uganda, in which children with single dose nevirapine exposure started nevirapine-based treatment at an older age of 1.6 years, there was no difference in response to therapy between children with and without prior single-dose nevirapine exposure[12]. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as <1 $\log_{10}$ 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 virologic 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, $p = 0.027$[13]. A comparison study of nevirapine versus lopinavir/ritonavir in children 6–36 months of age 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[14].

Body surface area has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid underdosing of nevirapine because a single point mutation may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance of nevirapine than older children and require a higher dosage to achieve equivalent drug exposure compared with children >8 years of age[7-8]. For that reason, the recommended dosing of nevirapine for children younger than 8 years old is 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children 8 years or older, the recommended dose is 120 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum of 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients based on two ongoing trials: VERxVE and TRANxITION. VERxVE 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. Both studies have shown equivalent efficacy, side effect, and CD4 profiles through 48 (VERxVE) and 24 weeks (TRANxITION)[15]. No data exist on the use of extended-release nevirapine in patients younger than 18 years of age.

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Rilpivirine (Edurant, TMC 278)

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

Formulations

Tablet: 25 mg

Dosing Recommendations

Neonate/infant dose:
Rilpivirine is not approved for use in neonates/infants.

Pediatric dose:
Rilpivirine is not approved for use in children.

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.
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Use rilpivirine with caution when coadministered 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 of rilpivirine 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, the patient's medication profile should be carefully reviewed for potential drug interactions with rilpivirine.

Major Toxicities:

- *More common:* Insomnia, headache, and rash.
- *Less common (more severe):* Depression or mood changes.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html).

Pediatric Use: The pharmacokinetics (PKs), 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 (NRTIs) in ARV-naive children ages 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)

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:

ATV is 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 of ATV in all children younger than 6 years or in treatment-experienced children who weigh less than 25 kg.

For children ≥6 to <18 years of age:

Weight (kg)	Once-Daily Dose*
Treatment-Naive ** Children Only	
15 to <25 kg	ATV 150 mg + RTV 80 mg, both once daily with food
Both Treatment Naive and Treatment-Experienced Children	
25 to <32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32 to <39 kg	ATV 250 mg + RTV 100 mg, both once daily with food
≥39 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Higher doses than those currently recommended may be required for some patients. See discussion under Pediatric Use.

** Data are insufficient to recommend this dose in treatment-experienced children who weigh less than 25 kg.

For treatment-naive pediatric patients who do not tolerate ritonavir (RTV): **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.**

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.
- 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 coadministered 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.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is coadmin-

Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children younger than 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).

Adolescent (≥18–21 years of age)/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.

istered 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. Coadministration of ATV with PPIs is not recommended in treatment-experienced patients.

- Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and patients with marked elevations in transaminases prior to treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of 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 CYP3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme UGT1A1. Atazanavir is a weak inhibitor of CYP2C8.
- Before atazanavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir.
- *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 (NNRTIs):* Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in treatment-experienced patients but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naive adults.
- *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 coadministered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and PPIs in adults are as follows:

- *Antacids:* Atazanavir concentrations are decreased when the drug is coadministered 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 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 + TD F 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 prior to 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 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 (SJS). 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 who are ≥6 years of age.

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-per-kg body weight or mg-per-meter^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 per meter^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 >13 years of age required atazanavir dosing of 620 mg per meter^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 plasms concentration (C_{min}) lower for the unboosted arms. Median doses of atazanavir in mg/m^2 body surface area 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 150ng/mL[2]. Higher target trough concentrations may be required in PI-experienced patients.

Summary of ATV 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 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 (TGs) were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs[3-4].

In a small single site study, 23 pediatric patients (median age 16 years) on combination antiretroviral therapy (cART) were switched to a once-daily ritonavir-boosted atazanavir-containing regimen because of virologic failure (12 patients) or for treatment simplification (11 patients)[5]. Twenty of the patients had previously received PI-based regimens with the median number of 2 atazanavir mutations acquired prior to switching to ATV/r. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine. Both tenofovir and didanosine are known to have PK interactions with atazanavir. In this study, atazanavir plasma concentrations were measured at 12–15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients 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)

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

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Dosing Recommendations

DRV should not be used without ritonavir (RTV).

Neonate/infant dose:
DRV is not approved for use in neonates/infants.

Pediatric dose:
DRV should not be used in pediatric patients <3 years of age.

3 to <6 years of age:
Safety and efficacy have not been established.

6 to <18 years of age and body weight ≥20 kg:

Weight (kg)	Dose DRV + RTV (both twice daily* with food)
≥20 to <30 kg	DRV 375 mg + RTV 50 mg (0.6 ml of 80 mg/ml)†
≥30 to <40 kg	DRV 450 mg + RTV 60 mg (0.8 ml of 80 mg/ml)†
≥40 kg	DRV 600 mg + RTV 100 mg

** Do not use once-daily dosing in children <12 years of age or in any patient <18 years of age who is treatment experienced. Once-daily dosing (DRV 800 mg + RTV 100 mg) may be used in treatment naive pediatric patients 12–18 years of age and body weight >40 kg (see Pediatric Use).*

† To enhance palatability, RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation, even though the RTV dose is higher.

Adolescent (≥18 years of age)/adult dose (treatment naive or antiretroviral [ARV] experienced with no DRV mutations):
DRV 800 mg + RTV 100 mg, both once daily with food.

Selected Adverse Events

- Skin rash (DRV has a sulfonamide moiety. Stevens-Johnson syndrome [SJS] and erythema multiforme have been reported.)
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Administer DRV with food, which increases 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 sulfa moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store DRV at room temperature (25°C or 77°F).

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing in patients with hepatic impairment:** DRV is primarily metabolized by the liver. No

Adolescent (≥18 years of age)/adult dose (treatment experienced with at least one DRV mutation):
DRV 600 mg + RTV 100 mg, both twice daily with food.

data exist 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). No pharmacokinetic (PK) data exist 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 CYP3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. There is the potential for multiple drug interactions with darunavir.
- Before darunavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and SJS, has been reported. Fever and elevated hepatic transaminases have been reported. Lipid abnormalities.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (e.g., hepatitis B or hepatitis C virus coinfection, baseline elevation in transaminases).

Resistance: The International 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/DRV.html).

Pediatric Use: Food and Drug Administration (FDA) approved for use in children 6 years of age and older as part of combination antiretroviral therapy (cART).

Initial pediatric pharmacokinetic (PK) evaluation was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric participants 6 to <18 years of age and weighing ≥20 kg. The participants had a median age of 14 years (range 6 to <18 years); 71% were male; and 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 2 non-protease inhibitor (PI) ARV drugs[1]. The study was a 2-part Phase II trial to evaluate the PKs and tolerance of darunavir/ritonavir in children. In Part I, a weight-adjusted dose of darunavir 9–15 mg/kg and riton-

avir 1.5–2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with AUC_{24h} of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult PK parameters. A pediatric dose 20%–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 11–19 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily. This resulted in darunavir AUC_{24h} of 123,276 ng*h/ml (range 71,850–201,520 ng*h/ml) and C_{0h} of 3,693 ng/mL (range 1,842–7,191 ng/ml), 102% and 114% of the corresponding PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation all patients were allowed to switch to ritonavir 100-mg capsules if desired to avoid the use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight band doses of darunavir/ritonavir were chosen as follows: 375/50 mg twice daily for body weight 20 to <30kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. This treatment was safe and effective.

Note that 27 of the 80 participants in this study[1] switched from the ritonavir liquid formulation to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. A separate study in 19 Thai children[2] (http://www.retroconference.org/2011/Abstracts/40772.htm) 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 PKs of those 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 6 years of age or weighing as little as 20 kg.

An investigational darunavir oral suspension has been studied in children 3 to <6 years of age and weighing 10 to <20 kg[3] (http://www.retroconference.org/2011/Abstracts/42411.htm). Higher than anticipated doses were required to achieve target drug exposures. Diarrhea and vomiting were the most common side effects. There was good efficacy through 48 weeks in this treatment-experienced population.

Although darunavir is approved for once-daily dosing in ARV-naive adults, it should not be used once daily in children younger than 12 years of age because of more rapid clearance and absence of pediatric data. However, once-daily dosing (DRV 800 mg + RTV 100 mg) may be considered in treatment naive adolescents 12–17 years of age and body weight >40 kg based upon a small study (N=12) that showed good Week 24 virologic responses and PK parameters similar to those seen in adults treated with once-daily darunavir[4].

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Fosamprenavir (FPV, Lexiva)

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

Formulations

Tablets: 700 mg FPV calcium

Oral suspension: 50 mg/mL

Dosing Recommendations

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

Pediatric dose (2–18 years of age):
Dosing regimen depends on whether patient is antiretroviral (ARV) naive or ARV experienced. Once-daily dosing is not recommended for pediatric patients.

ARV-naive patients (2–5 years of age):
Unboosted (without ritonavir [RTV]):
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily.

ARV-naive patients (>6–18 years of age):
Unboosted (without RTV):
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily.

or

Boosted with RTV:
FPV 18 mg/kg (maximum dose 700 mg) +
RTV 3 mg/kg (maximum dose 100 mg), both twice daily.

ARV-experienced patients (>6–18 years of age):
Boosted with RTV:
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily.

Note: When administered without RTV, the adult regimen of FPV tablets (FPV 1,400 mg twice daily) can be used for patients weighing ≥47 kg ***or*** when administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Adolescent (>18 years of age)/adult dose:
Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (FPV has a sulfonamide moiety. Stevens-Johnson syndrome [SJS] 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 FPV oral suspension well prior to use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as FPV is absorbed.

ARV-naive patients:
Unboosted (without RTV), twice-daily regimen:
FPV 1,400 mg twice daily.
Boosted with RTV, twice-daily regimen:
FPV 700 mg + RTV 100 mg, both twice daily.
Boosted with RTV, once-daily regimen:
FPV 1,400 mg + RTV 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 in PI-experienced patients.

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 1,400 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.

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 fosamprenavir is administered, the 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 SJS, 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 pediatric patients (30%–56%) than in adult patients (10%–16%)[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/APV_FPV.html).

Pediatric Use: Fosamprenavir is Food and Drug Administration (FDA) approved for use in children as young as 2 years of age.

Fosamprenavir was studied in two open-label trials in both treatment-experienced and treatment-naive pediatric patients 2–18 years of age[2-3]. In one study, twice-daily dosing regimens (with or without ritonavir) were evaluated in combination with other ARV agents[3]. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count. In the second trial, once-daily fosamprenavir/ritonavir was studied[2]. Following information about suboptimal response to once-daily dosing in treatment-experienced adults, pediatric patients were allowed to switch to twice-daily therapy; however, few patients (10 of 69) opted to switch to twice-daily therapy (median time to switch: 45 weeks). At 24 and 48 weeks of therapy, HIV RNA was <400 copies/mL in 66% and 47% among PI-naive subjects, respectively, and 57% and 43% among PI-experienced subjects, respectively. These 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.

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Indinavir (IDV, Crixivan)

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

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose:
IDV is not approved for use in neonates/infants.

IDV should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
IDV is 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) has been studied in children (see Pediatric Use).

Adolescent/adult dose:
800 mg IDV + 100 or 200 mg RTV every 12 hours.

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal (GI) 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

- Administer IDV on an empty stomach 1 hour before or 2 hours after a meal (or administer with a light meal). When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If coadministered with didanosine (ddI), give 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 indinavir metabolism. There is potential for multiple drug interactions.
- Before indinavir is administered, the 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 redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life threatening in rare cases).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

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/IDV.html).

Pediatric Use: Indinavir has not been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Even though indinavir was one of the first protease inhibitors (PIs) 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 a dose of 500–600 mg of unboosted indinavir per meter^2 of body surface area given every 8 hours results in peak blood concentrations and areas under the curve (AUC) 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[2-17]. Studies in small groups of children of a range of ritonavir-boosted indinavir doses have shown that 500 mg indinavir per meter^2 of body surface area plus 100 mg ritonavir per meter^2 of body surface area twice daily is probably too high[14], that 234–250 mg indinavir per meter^2 of body surface area plus low-dose ritonavir twice daily is too low[18-19], and that 400 mg indinavir per meter^2 of body surface area plus 100–125 mg ritonavir per meter2 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[2,5,19].

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%)[20]. This is likely due to the difficulty in maintaining hydration adequate to minimize risk of nephrolithiasis 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 the risk of renal dysfunction among children receiving combination antiretroviral therapy (cART) with indinavir[21].

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Lopinavir/Ritonavir (LPV/r, Kaletra)

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

Formulations

Pediatric oral solution: 80 mg/20 mg LPV/r/mL (contains 42.4% alcohol by volume)

Pediatric Tablets: 100 mg/25 mg LPV/r

Tablets: 200 mg/50 mg LPV/r

Dosing Recommendations

Neonate dose (age <14 days):
No data on appropriate dose or safety of LPV/r in this age group. Do not administer to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

Infant dose (age 14 days–12 months) in individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV):
Once-daily dosing is **not** recommended.

The recommended dose of the oral solution is 300 mg/75 mg LPV/r per m^2 of body surface area twice daily or 16 mg/4 mg LPV/r per kg of body weight twice daily.

NOTE: Use of 300 mg/75 mg LPV/r per m^2 of body surface area in infants 12 months of age 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 Pediatric Use).

Pediatric dose (age >12 months–18 years) in individuals not receiving concomitant NVP, EFV, FPV, or NFV:
Once-daily dosing is **not** recommended.

Body surface area dosing:
230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily 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 the patient to "grow into" the 230 mg/m^2 dosage as they gain weight over time (see Pediatric Use).

300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily is used by many clinicians, espe-

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*).

Special Instructions

- LPV/r tablets can be administered without regard to food, but recognize that administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food. A high-fat meal increases absorption, especially of the liquid preparation.
- The poor palatability of LPV/r oral solution can sometimes be partially masked 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°

cially for patients previously treated with ARV drugs (see Pediatric Use).

Weight-based dosing:
<15 kg: 12 mg/3 mg LPV/r per kg of body weight per dose twice daily.

≥15 kg to 40 kg: 10 mg/2.5 mg LPV/r per kg of body weight per dose twice daily.

≥40 kg: 400 mg/100 mg LPV/r per dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents Without Concomitant NVP, EFV, FPV, or NFV.

Body Weight (kg)	Body Surface Area (m^2)	Recommended Number of 100 mg/ 25 mg LPV/r Tablets Given Twice Daily
15 to 25 kg	≥0.6 to <0.9 m^2	2
>25 to 35 kg	≥0.9 to <1.4 m^2	3
>35 kg	≥1.4 m^2	4 (or two 200 mg/ 50 mg LPV/r adult tablets)

Pediatric dose (age >12 months to 18 years) For individuals receiving concomitant NVP, EFV, FPV, or NFV.
(These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs and/or in treatment-experienced patients in whom reduced susceptibility to LPV is suspected, such as patients with prior treatment with other protease inhibitors [PIs].)

Do not administer LPV/r with NVP, EFV, FPV, or NFV in infants 6 months of age or younger.

Once-daily dosing is **not** recommended.

Body surface area dosing:
300 mg/75 mg LPV/r/ per m^2 of body surface area per dose twice daily.

Weight-based dosing:
<15 kg: 13 mg/3.25 mg LPV/r per kg of body weight per dose twice daily.

to 46ºF) LPV/r oral solution remains stable until the expiration date printed on the label.

- LPV resistance-associated substitutions: LPV/r can be administered once daily (800 mg/200 mg) in adults with fewer than three LPV resistance-associated substitutions. Once-daily administration of LPV/r is not recommended for adult patients with three or more of the following LPV resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P 450 3A4 (CYP3A4) 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 (PK) enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

≥15 kg to 45 kg: 11 mg/2.75 mg LPV/r per kg of body weight per dose twice daily.

≥45 kg: Use adult dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children With Concomitant NVP, EFV, FPV, or NFV

Body Weight (kg)	Body Surface Area (m^2)	Recommended Number of 100 mg/ 25 mg LPV/r Tablets Given Twice Daily
15 to 20 kg	≥0.6 to <0.8 m^2	2
>20 to 30 kg	≥0.8 to <1.2 m^2	3
>30 to 45 kg	≥1.2 to <1.7 m^2	4 (or two 200 mg/50 mg LPV/r tablets)
>45 kg	≥1.7 m^2	4 or 6 (or two 200 mg/50 mg LPV/r adult tablets)*

**The higher dose may be considered in treatment-experienced patients when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing.*

NOTE: In children, use of 230 mg/57.5 mg LPV/r per m^2 of body surface area (when not coadministered with NVP, EFV, FPV, or NFV) or use of 300 mg/75 mg LPV/r per m^2 of body surface area (when coadministered with NVP, EFV, FPV, or NFV) is associated with area under the curve (AUC) LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults. Therefore, some clinicians may choose to initiate therapy with higher doses of LPV/r when coadministered with these drugs or in PI-experienced pediatric patients who may have reduced PI susceptibility (see Pediatric Use).

Adult dose(age >18 years):
In patients with fewer than three LPV-associated mutations (see Special Instructions for list):

800 mg/200 mg LPV/r once daily; **or**

400 mg/100 mg LPV/r twice daily.

Do **not** use once-daily dosing in children or adolescents. Once-daily dosing should not be used in

patients receiving concomitant therapy with NVP, EFV, FPV, or NFV.

In patients with three or more LPV-associated mutations (see Special Instructions for list):

400 mg/100 mg LPV/r twice daily.

In patients receiving concomitant NVP, EFV, FPV, or NFV):
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:* Lopinavir/ritonavir is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before lopinavir/ritonavir is administered, the 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):* Lipodystrophy.
- *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 bradyarrhthymias and cardiac dysfunction[2-3, 4]; and lactic acidosis, acute renal failure, central nervous system (CNS) 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 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.

For 12 children 6 months to 12 years of age 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 6 months to 12 years of age 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]. Therefore, the Panel recommends using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area in infants up to 12 months of age; in addition, some clinicians may choose to initiate therapy in children 12 months to 12 years of age 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[6].

The PK behavior of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily was evaluated in infants younger than 6 weeks of age[7] and infants 6 weeks to 6 months of age[8]. PK values found in these studies are compared to those in older children[5] and adults[9] 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]	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	101	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	4.3	2.7	2.5
C_{min} mcg/mL	5.5	3.4	6.5	3.8	2.0	1.4

Even at this higher dose, predose (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 6 weeks of age or younger compared

with those between ages 6 weeks and 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 the 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.

For children, as in adults, the lopinavir C_{trough} is further reduced by concurrent treatment with NNRTIs or concomitant fosamprenavir or nelfinavir and, as in adults, higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL[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 children with HIV infection treated with the combination of lopinavir/ritonavir using an increased dose of 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus efavirenz 14 mg/kg of body weight per dose once daily, the median 12-hour lopinavir trough was 5.7 mcg/mL, but there was 34-fold interindividual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV[12]. A PK study in 20 children 10 to 16 years of age treated with the combination of lopinavir/ritonavir 300 mg/75 mg per m^2 of body surface area twice daily plus efavirenz 350 mg/m^2 of body surface area once daily showed adequacy of the lopinavir trough values[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 interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21 of 59 patients (35.6%)[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 children with HIV and severe immune suppression[19-20], although patients with greater prior exposure to ARVs 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 prior to a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC50). The ratio of C_{trough} to EC50 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 EC50 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 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/ri-

tonavir are likely to be inadequate for treatment-experienced children and underscore the potential utility of TDM in children previously treated with PIs 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 taking 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 in Thailand, 21 of 54 children used cut (not crushed) pills with no negative impact on PK 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%[29-30]. The poor weight gain associated with lopinavir/ritonavir is of uncertain cause.

The poor palatability of the oral solution can be a significant challenge to medication adherence for some children and families. Administration of the medication before or after ice chips, sweet or tangy foods, chocolate syrup, or peanut butter, for example, or with flavorings added to it by a pharmacy may partially improve taste.

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Nelfinavir (NFV, Viracept)

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

Formulations

Powder for oral suspension: 50 mg/1 level gram scoopful (200 mg/1 level teaspoon)
(Oral powder contains 11.2 mg phenylalanine per gram of powder.)

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/infant dose:
NFV should not be used for treatment in children <2 years of age.

(See the perinatal guidelines for recommendations on use of NFV for prevention of mother-to-child transmission [PMTCT] of HIV.)

Pediatric dose (2–13 years of age):
45–55 mg/kg twice daily.

Adolescent/adult dose:
1,250 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 [TDM] 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 coadministered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- NFV powder for oral suspension may be mixed with water, milk, pudding, ice cream, or formula; refrigerated mixture is stable for up to 6 hours.
- Do not mix powder with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of NFV oral powder. The scoop provided with the powder should be used for measuring. The powder and solution should be mixed in another container.
- 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 coadministration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.
- Before nelfinavir is administered, carefully review the 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 two nucleoside reverse transcriptase inhibitors (NRTIs) in children >2 years of age. Nelfinavir is not recommended for treatment in children <2 years of age. Nelfinavir may be considered for neonatal prophylaxis of perinatal transmission in HIV-exposed infants in selected circumstances[1]. (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).

Nelfinavir in combination with other antiretroviral (ARV) drugs has been extensively studied in HIV-infected children[2-9]. In randomized trials of children 2–13 years of age 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 (NNRTIs) as well as highly variable drug exposure and poor patient acceptance of available formulations[10-11].

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve [AUC] increased by as much as 5-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, poor acceptance of pediatric formulation, and difficulties in taking nelfinavir with sufficient food to improve bioavailability.The pediatric powder formulation is 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[2]. 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[16].

Antiviral response to nelfinavir is significantly less in children younger than 2 years than in older children[7, 9, 17]. Infants have even lower drug exposures and higher variability in plasma concentrations than children who weigh <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[18-19]. For these reasons, nelfinavir is not recommended for use in children younger than 2 years. In older children and adolescents, it is unclear when to change from the recommended 45–55 mg/kg twice-daily dose to the adult dose of 1,250 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[20-22]. 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 concentrations <0.8 mcg/mL[23]. 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[23]. TDM of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir[20, 24]. Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of TDM and appropriate dose adjustment might be even greater for children. Better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing.[15, 25]

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Ritonavir (RTV, Norvir)

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 (PIs) 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 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

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.

To increase tolerance of RTV oral solution in children:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.

- Before administration, give the child ice chips, a popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds or give the child peanut butter to coat the mouth.
- After administration, give the child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- **Dosing of RTV in patients with hepatic impairment:** RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are not available 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 CYP3A. There is potential for multiple drug interactions with ritonavir.
- Before ritonavir is administered, the 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[1-2].

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias, lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.

Resistance: Resistance to ritonavir is not clinically relevant when the drug is used as a PK enhancer of other 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 an antiretroviral (ARV) regimen for therapy 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 ARV 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 the 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 compared with efavirenz or lopinavir/ritonavir[3-4]. Additionally, 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 350–450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group[5-16].

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[17]. 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[18-19]. Coadministration 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 coadministering 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)

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

Formulations

Hard-gel capsules (HGC): 200 mg

Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/infant dose:
SQV is not approved for use in neonates/infants.

Pediatric dose:
SQV is not approved for use in children.

Investigational doses in treatment-experienced children:
SQV must be boosted with ritonavir (RTV):

<2 years of age:
No dose has been determined.

*≥2 years of age (**conditional dosing based on limited data, see Pediatric Use**):*

Weight (kg)	Dose SQV + RTV
5 to <15 kg	SQV 50 mg/kg + RTV 3 mg/kg, both twice daily
15 to 40 kg	SQV 50 mg/kg + RTV 2.5 kg/kg, both twice daily
≥40 kg	SQV 50 mg/kg + RTV 100 mg, both twice daily

≥7 years of age in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (conditional dosing based on limited data, see Pediatric Use):

SQV 750 mg/m^2 (max 1,600 mg) or SQV 50 mg/kg have been used in combination with LPV/r, both twice daily.

Adolescent (≥16 years of age)/adult dose:
SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

SQV in combination with RTV:

SQV 1,000 mg + RTV 100 mg, both twice daily.

Selected Adverse Events

- Gastrointestinal (GI) 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, ventricular tachycardia (torsades de pointes) have been reported

Special Instructions

- Administer SQV within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions in patients using SQV; advise patients to use sunscreen or protective clothing.
- Pretherapy electrocardiogram (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval or in patients who are receiving other drugs that can prolong the 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 with saquinavir.
- Before saquinavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and torsades de pointes.

Resistance: The International 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/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 younger than 2 years of age and 13 children between the ages of 2 and 5 years using a saquinavir dose of 50 mg/kg twice daily with boosting ritonavir revealed that drug exposure was lower in children younger than 2 years of age whereas drug exposure was adequate in children 2 to 5 years of age[7]. For this reason, saquinavir should not be given to children younger than 2 years of age until an appropriate dose is identified. In children ≥2 years of age, a dose of 50 mg/kg twice daily (maximum dose = 1,000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 to 40 kg) resulted in area under the curve (AUC) and steady state trough concentration (C_{trough}) values similar to those in older children[8-9] and adults. Because a pediatric formulation is not available, in 1 study saquinavir was formulated by breaking open the 200-mg HGCs and mixing capsule contents with sugar syrup, jam, or baby formula. Sorbitol syrup was used for patients with diabetes or glucose intolerance[7].

Both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens are promising in the salvage therapy setting 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 1,600 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 of age, 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 4 patients (decreased in 3, increased in 1)[10].

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance. In this group, saquinavir was dosed at 50 mg/m^2 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 (TDM) 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 (TC) and high-density lipoprotein (HDL) 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 (msec), refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An ECG is recommended before initiation of therapy with saquinavir and should be considered during therapy.

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Tipranavir (TPV, APTIVUS)

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

Formulations

Oral solution: 100 mg TPV/mL with 116 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 (<2 years of age):

TPV is not approved for use in children <2 years of age.

Pediatric dose (2–18 years of age):

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:

TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily.

Selected Adverse Events

- Rare cases of fatal and nonfatal intracranial hemorrhage (ICH)
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer TPV with food.
- TPV oral solution contains 116 IU of vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- TPV contains a sulfonamide component 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 oral TPV capsules in a refrigerator at 2°–8°C (36°–46°F). Capsules can be kept at room temperature (maximum of 25°C or 77°F) if used within 2 months after the bottle is first opened.
- 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 of TPV in patients with renal impairment:** No dose adjustment is required.
- **Dosing of TPV in patients with hepatic impairment:** No dose adjustment is 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, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities:

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Laboratory abnormalities associated with tipranavir use include elevated transaminases, cholesterol, and triglycerides (TGs).
- *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 ICH.

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/TPV.html).

Pediatric Use: Tipranavir is Food and Drug Administration (FDA) approved for use in children ≥2 years of age who are treatment experienced and infected with HIV strains resistant to more than one 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 2 years of age 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 per m^2 body surface area (high dose, 57 patients) twice daily plus optimized background therapy (OBT). All children initially received the oral solution but patients who were 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 the age of the child[2]. At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of patients receiving the high dose had viral loads <400 copies/mL. The groups did not differ in the 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 group of patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 cell count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, side effects were similar between treatment groups. Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs due to adverse events. The most common adverse events were gastrointestinal (GI) disturbances; 37% of participants had vomiting and 24% had diarrhea. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase [GGT] and creatine phosphokinase [CPK]) 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 the 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 the 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, the high-dose of tipranavir/ritonavir has been recommended.

PKs of the liquid formulation at steady state were assessed[3]. For children ages 2 to younger than 12 years, tipranavir trough concentrations for pediatric patients receiving tipranavir/ritonavir 290/115 mg per m^2 body surface area were consistent with tipranavir trough concentrations achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children 12–18 years of age required a higher dose (375/150 mg/m^2 body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard tipranavir/ritonavir dose. Population 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 per ml of solution. The recommended dose of tipranavir (14 mg per kg body weight) results in a vitamin E dose of 16 IU per kg body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. 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)

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 (6–16 years of age):
Children <6 years of age:
ENF is not approved for use in children <6 years of age.

Children ≥6 years of age:
2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Adolescent (>16 years of age)/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. Rechallenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous injections. ENF injection instructions are provided with convenience kits.
- After adding sterile water to vial of ENF, allow 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 subcutaneously; severity of reactions increases if given intramuscularly.
- Give each injection of ENF 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, pruritis, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3–7 days, but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association).
- *Rare:* HSRs in <1% of patients, 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% of children in certain subgroups of patients in pediatric studies)[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/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 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 (e.g., maraviroc).

A single-dose pharmacokinetic (PK) evaluation study of enfuvirtide given subcutaneously to 14 HIV-infected children 4–12 years of age (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 subcutaneously to an adult (1,000 ng/mL)[3]. In a second pediatric study of 25 children 5–16 years of age, 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 6–16 years of age is 2 mg/kg (maximum 90 mg) administered subcutaneously twice daily. Further data are needed for dosing in children <6 years of age.

The safety and antiretroviral (ARV) activity of twice-daily subcutaneous enfuvirtide administration at 60 mg/m^2 per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children 4–12 years of age 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 subcutaneously, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children 3–16 years of age 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 median increase in CD4 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 (<11 years of age) compared with adolescents. Median increases in CD4 count were 257 cells/mm3 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)

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:
MVC is not approved for use in neonates/infants.

Pediatric dose:
MVC is not approved for use in children <16 years of age. A dose finding study is under way.

Adolescent (>16 years of age)/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
- Orthostatic hypotension

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.
- Give MVC without regard to food.
- Instruct patients/caregivers 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 maraviroc is administered, the 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 (e.g., 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 (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance: The International Antiviral 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 (PKs), safety, and efficacy of maraviroc in patients <16 years of age have not been established. A dose finding study is under way in children 2-17 years of age[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.

References:

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Appendix A: Pediatric Antiretroviral Drug Information

Integrase Inhibitors

Raltegravir (RAL, Isentress)

Raltegravir (RAL, Isentress)

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

Formulations

Tablets: 400 mg (poloxamer tablet)

Dosing Recommendations

Neonate/infant dose:
RAL is not approved for use in neonates/infants.

Pediatric dose:
RAL is not approved for use in children <16 years of age.

Investigational dose in children >6 years of age (and body weight >25 kg):
400 mg twice daily.

Adolescent (≥16 years of age)/adult dose:
400 mg twice daily.

Selected Adverse Events

- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Give RAL without regard to food.

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 is necessary.

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

- *Metabolism:* The major mechanism of clearance of raltegravir is mediated through glucuronidation by UGT1A1. Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir, while inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Before raltegravir is administered, the 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:* CPK elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash and Stevens-Johnson syndrome (SJS) have been reported. Thrombocytopenia.

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/cgi-bin/INIResiNote.cgi).

Pediatric Use: Raltegravir is not approved by the Food and Drug Administration (FDA) for use in children <16 years of age. Raltegravir in combination with other antiretroviral (ARV) agents is currently being evaluated in IMPAACT 1066, a Phase I/II study in HIV-infected children, in which intensive pharmacokinetic (PK) evaluations were performed on Days 7–12 after raltegravir was added to a stable ARV backbone.

Because there is no food or fasting requirement with licensed use of raltegravir in adults, intensive PK evaluations were initially performed in children 12 to <19 years of age, with raltegravir administered with food[1]. However, because the effect of food made comparisons to data obtained in fasting adults difficult, the study was then amended to conduct PK evaluations in the fasted state. This led to selection of a dose of 400 mg twice daily of the approved formulation (poloxamer tablet) in children >12 to <19 years of age for longer term evaluation of safety and efficacy[2]. Preliminary data from 43 participants in this age group after 24 weeks of treatment with raltegravir plus an optimized background regimen demonstrated that 71% of participants had either a viral load <400 copies/mL or a 1.0 $_{\log}$ decrease in viral load; 53% had a viral load <50 copies/mL; and the median CD4 count increase was 111 cells/mm^3. Four Grade 3 adverse reactions (2 neutropenic episodes, 1 liver enzyme elevation, and 1 behavioral change) were judged possibly related to raltegravir; no participants discontinued therapy due to toxicity[3].

Children ≥6 to <12 years of age were initially treated at a dose of 8 mg/kg twice daily. Evaluation of the PK data in 10 participants again led to choosing a uniform dose of 400 mg twice daily for children who weighed >25 kg. At 12 and 24 weeks of therapy, 78% and 67% of 14 children in this cohort had a viral load <400 copies/mL[4]. No unusual toxicity has been seen so far[4-5].

In addition to the approved adult formulation (400-mg poloxamer tablet), two investigational raltegravir preparations are being evaluated in IMPAACT 1066: chewable ethylcellulose tablets in children >2 to <12 years of age[6] and an oral suspension for children <2 years of age. PK studies of the chewable tablet have been performed and long-term follow-up is ongoing[6-7].

In the French Expanded Access Program, 23 heavily treatment experienced youth 12–17 years of age who acquired HIV infection perinatally have been treated with raltegravir and other active agents, including etravirine and darunavir, with good virologic and immunologic results[8-9].

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Appendix B: Key to Acronyms

3TC	lamivudine
AAP	American Academy of Pediatrics
ABC	abacavir
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APV	amprenavir
ART	antiretroviral therapy antiretroviral treatment
ART-CC	ART Cohort Collaboration
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
CHIPS	Collaborative HIV Pediatric Study
CK	creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system

CPK	creatine phosphokinase
CrCl	creatinine clearance
CT	computed tomography
	continuous therapy
CVD	cardiovascular disease
CYP	cytochrome P
CYP450	cytochrome P450
CYP3A4	cytochrome P450 3A4
d4T	stavudine
ddI	didanosine
DM	diabetes mellitus
D/M	dual-mixed (tropic)
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy
DRESS	drug reaction 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 immunosorbant assay
EM	erythema multiforme
ENF	enfuvirtide
ETR	etravirine
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FPV	fosamprenavir
FTC	emtricitabine

FXBC	François-Xavier Bagnoud Center
G6PD	glucose-6-phosphate dehydrogenase
GAZT	AZT glucuronide
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
HGC	hard-gel capsule
HHS	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
IC50	inhibitory concentration
ICH	intracranial hemorrhage
IDV	indinavir
IDSA	Infectious Disease Society of America
IFA	immunofluorescent antibody (assay)
IgE	immunoglobulin E
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient

IRIS	immune reconstitution inflammatory syndrome
IU	International Unit
IUD	intrauterine device
IVIG	intravenous immunoglobulin
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
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside 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
PG	plasma glucose
Pgp	p-glycoprotein
PI	protease inhibitor
PIDS	Pediatric Infectious Disease Society
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PPI	proton-pump inhibitor
PR	protease
PUFA	polyunsaturated fatty acid
RAL	raltegravir
RBV	ribavarin
RPG	random plasma glucose
RT	reverse transcriptase
RTV	ritonavir
SJS	Stevens-Johnson syndrome
SQV	saquinavir
STI	sexually transmitted infection structured treatment interruption
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

TMC-278	rilpivirine
TMP-SMX	trimethoprim sulfamethoxazole
TPV	tipranavir
TPV/r	tipranavir/ritonavir
UA	urinalysis
UGT1A1	uridine diphosphate gluconyltransferase
ULN	upper limit of normal
USPHS	U.S. Public Health Service
WHO	World Health Organization
ZDV	zidovudine