Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

February 23, 2009

Developed by the Working Group 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**.

What's New in the Document?

The following changes have been made to the July 29, 2008 version of the guidelines. Key new updates are highlighted throughout the document.

Format Changes

This revision is developed under a new format, whereby the relevant tables and references for each section are incorporated into the body of the document. Some larger tables and figures are placed in Appendix A at the end of the document. A separate PDF file with all the tables can be found at the AIDS*info* Web site.

Content Changes

The key changes to the different sections of the guidelines are outlined below:

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

- Although darunavir is recently approved for treatment of infected children over age 6 years, because the currently available formulations require a high pill burden to provide adequate dosing for children weighing under 40 kg and several alternative options are available for initial treatment, darunavir is not currently recommended for initial therapy in children. However, low-dose ritonavir boosted darunavir and tipranavir have utility as components of secondary treatment regimens for children who fail initial therapy.
- **Table 7**: Updated information on darunavir included.

Antiretroviral Treatment Failure in Infants, Children, and Adolescents

- The former section "Management of the Treatment Experienced Child" has been completely revised into a more detailed section on management of treatment failure in children.
- Definitions of viral and immune failure have been updated.
- A detailed discussion of discordance between viral, immune, and clinical responses has been added.
- A new table (**Table 13**) on Assessment of Antiretroviral Treatment Failure has been added to provide more explicit guidance on evaluation of a child with treatment failure.
- Revised sections on Approach to the Management of Treatment Failure and Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance have been added.
- A new section on the Use of Antiretroviral Agents Not Approved for Use in Children has been added.
- **Table 15** has the addition of therapeutic target trough concentrations for maraviroc and tipranavir.

Antiretroviral Drug Resistance Testing

- The section has been updated and includes tropism assays.

Appendix B: Characteristics of Available Antiretroviral Drugs

- Updates have been added for the drugs abacavir, didanosine, lamivudine, stavudine, zidovudine, nevirapine, atazanavir, darunavir, ritonavir, and maraviroc.

Supplement I: Pediatric Antiretroviral Drug Information

- Updates have been added to the overview, and to drug sections on abacavir, didanosine, lamivudine, zidovudine, efavirenz, darunavir, ritonavir, maraviroc, and raltegravir.

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These guidelines were developed by:
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Introduction (Updated October 26, 2006)

These guidelines address issues specific to the use of antiretroviral therapy for HIV-infected infants, children, and pre-pubertal adolescents. The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, a working group of the Office of AIDS Research Advisory Council, reviews new data on an ongoing basis and provides regular updates to the guidelines, which are available at **http://AIDS*info*.nih.gov**. Also available at this Web site are updated guidelines for HIV-infected post-pubertal adolescents and adults *[1]*. As these guidelines were developed for the United States, they may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings at http://www.who.int/hiv/pub/guidelines/art/en/index.html.

In 1993, the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, composed of specialists caring for HIV-infected infants, children, and adolescents, was convened by the François-Xavier Bagnoud Center (FXBC), University of Medicine and Dentistry of New Jersey (http://www.fxbcenter.org/). Since 1998, the Working Group has held monthly conference calls to review new data. Proposed changes to the pediatric treatment guidelines are reviewed by the Working Group and incorporated as appropriate. All revisions are summarized and highlighted on the AIDS*info* Web site and posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Working Group prior to finalization. Comments can be sent to aidsinfowebmaster@aidsinfo.nih.gov.

Since the Working Group developed the initial guidelines in 1993, dramatic advances in medical management have followed the results of clinical trials of antiretroviral combination therapies in children. HIV mortality in children has decreased by over 80%-90% since the introduction of protease inhibitor-containing combinations, and opportunistic and other related infections have significantly decreased in HIV-infected children in the era of highly active antiretroviral therapy (HAART) *[2-7]*. Advances from clinical trials and in laboratory monitoring, including resistance testing and the ability to measure antiretroviral drug levels, have enabled clinicians to more carefully choose very effective initial regimens while preserving selected drugs and drug classes for second- or third- line regimens. Therapeutic strategies continue to focus on early initiation of antiretroviral regimens capable of maximally suppressing viral replication to prevent disease progression, preserve immunologic function, and reduce the development of resistance. At the same time, availability of new drugs and drug formulations has led to regimens that improve adherence with less frequent dosing schedules. Improved monitoring and dosing schedules have also led to a decrease in drug failure due to toxicity. The use of antiretroviral therapy during pregnancy in HIV-infected women has resulted in a dramatic decrease in the transmission rate to infants, which is currently less than 2% in the United States, and the number of infants with AIDS in the United States continues to decline *[8]*. Children living with HIV infection are, as a group, growing older, bringing new challenges of adherence, drug resistance, and management of multiple drugs.

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

- Acquisition of infection through perinatal exposure for many infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to zidovudine and other antiretroviral medications in most perinatally infected children;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants under age 18 months;
- Age-specific differences in CD4 cell counts;
- Changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
- Differences in the clinical and virologic manifestations of perinatal HIV infection secondary to the occurrence of primary infection in growing, immunologically immature persons; and
- Special considerations associated with adherence to antiretroviral treatment for infants, children, and adolescents.

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

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 *[9-11]*. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*
- The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all antiretroviral drugs produced.
- Although some information regarding the efficacy of antiretroviral drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children.
- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a specialist in pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted.
- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families requires a multidisciplinary team approach that includes physicians, nurses, dentists, social workers, psychologists, nutritionists, outreach workers, and pharmacists.
- Health care providers considering antiretroviral treatment for infants, children, or adolescents should consider certain factors influencing adherence to therapy, including:
  - availability and palatability of drug formulations;
  - impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food;
  - ability of the child's caregiver or the adolescent to administer complex drug regimens and availability of resources that might be effective in facilitating adherence; and
  - potential for drug interactions.
- The choice of initial antiretroviral regimen should include consideration of factors that may limit future treatment options, such as the presence of or potential for the development of antiretroviral resistance. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition are all essential in the care of HIV-infected children, as they may significantly influence quality of life; these issues are addressed in **Supplement II: Managing Complications of HIV Infection**.

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

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Identification of Perinatal HIV Exposure

(Updated February 28, 2008)

Working Group Recommendations:

- **Universal counseling and voluntary HIV testing early in pregnancy, including opt-out testing, is recommended as standard of care for all pregnant women in the United States.**
- **Repeat HIV testing is recommended in the third trimester for women at high risk of HIV infection who have negative HIV antibody tests earlier in pregnancy.**
- **Rapid HIV antibody testing is recommended to screen women who are seen at labor and have undocumented HIV status to allow intrapartum antiretroviral prophylaxis to be initiated prior to delivery in women identified as HIV-infected.**
- **Women who have not been tested for HIV prior to or during labor should be offered rapid testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing, with counseling and consent of the mother unless state law allows testing without consent. This allows initiation of antiretroviral prophylaxis soon after delivery for infants born to HIV-infected women, counseling of HIV-infected women not to breastfeed their infant, and linkage to HIV-related medical care and services for both mother and child.**

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 Working Group, 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 *[1-5]*. An opt-out approach notifies a pregnant woman that HIV testing will be performed as part of routine care unless she chooses not to be HIV-tested *[6]*.

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

- HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infections for their own health;
- Provision of antiretroviral chemoprophylaxis during pregnancy, during labor, and to the newborn to reduce the risk of HIV transmission from mother to child *[7]*;
- Counseling of HIV-infected women about the indications for and potential benefits of scheduled cesarean section delivery to reduce perinatal HIV transmission *[7,8]*;
- Counseling of HIV-infected women about the risks for HIV transmission through breast milk and advising against breast feeding in the United States and other countries where safe alternatives to breast milk are available *[9]*;
- Initiation of prophylaxis against *Pneumocystis* pneumonia (PCP) in all HIV-exposed infants with indeterminate HIV infection status or who have documented HIV infection beginning at age 4 to 6 weeks *[10]*; and
- Early diagnostic evaluation of HIV-exposed infants to permit early initiation of antiretroviral therapy in infected infants *[11]*.

REPEAT HIV TESTING IN THE THIRD TRIMESTER

Repeat HIV testing is recommended in the third trimester, preferably <36 weeks gestation, for women with initially negative HIV antibody tests who are at high risk of HIV infection, and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria: women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women age 15–45 years; women who receive health care in facilities in which prenatal screening identifies at least

one HIV-infected pregnant woman per 1,000 women screened; women who are known to be at high risk for acquiring HIV (e.g., injection drug users or partners of injection drug users, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than one sex partner during this pregnancy or diagnosis of a new sexually transmitted infection during pregnancy); and women who have signs or symptoms of acute HIV infection *[4,12,13]*. Women who have declined testing earlier in pregnancy should have testing offered again during the third trimester. There is evidence that the risk of HIV acquisition may be significantly higher during pregnancy than in the postpartum period *[14]*.

RAPID HIV TESTING DURING LABOR IN WOMEN WITH UNKNOWN HIV STATUS

Use of rapid test kits or an expedited enzyme-linked immunosorbent assay (ELISA) to detect HIV antibody is recommended to screen women who are seen at labor and have undocumented HIV status in order to identify HIV exposure in their infants *[4,11,13]*. Any hospital offering intrapartum care should have rapid HIV testing available and should have in place policies and procedures to assure that staff are prepared to provide patient education about rapid HIV testing; that appropriate antiretroviral medications are available whenever needed; and that follow-up procedures for women found to be HIV-infected and their infants are in place. Rapid tests have been found to be feasible, accurate, timely, and useful in signaling the need for immediate intrapartum and neonatal antiretroviral prophylaxis and in reducing perinatal HIV transmission *[15]*. Results of rapid tests can be obtained within minutes to a few hours and are more accurate than standard ELISA antibody testing *[16,17]*. A positive rapid HIV test result must be followed by a confirmatory test such as a Western blot (or immunofluorescent antibody [IFA]); a standard ELISA should not be used as a confirmatory test for a rapid HIV antibody test *[17]*. A negative single rapid test does not need confirmation. The immediate initiation of antiretroviral prophylaxis for prevention of mother-to-child HIV transmission is strongly recommended while awaiting confirmatory testing results after an initial positive rapid HIV test *[1,5,7]*.

HIV COUNSELING AND TESTING DURING POSTNATAL PERIOD

Women who have not been tested for HIV prior to or during labor should be offered rapid testing during the immediate postpartum period, or their newborns should undergo rapid HIV antibody testing, with counseling and consent of the mother unless state law allows testing without consent *[1,4,18,19]*. Because neonatal antiretroviral chemoprophylaxis should be initiated as soon as possible after birth to be effective in preventing mother-to-child transmission, use of rapid HIV antibody assays or expedited ELISA testing to allow prompt identification of HIV-exposed infants is critical. It is strongly recommended that infant antiretroviral prophylaxis be initiated while awaiting confirmatory testing results after an initial positive rapid test in the mother or the infant, and women with positive rapid HIV test results should be advised not to initiate breastfeeding pending results of confirmatory testing. If the confirmatory test is negative, the infant antiretroviral prophylaxis can be discontinued and the mother can initiate breastfeeding. Mechanisms should be developed to facilitate rapid HIV screening for infants who have been abandoned and are in the custody of the state.

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Diagnosis of HIV Infection in Infants

Working Group Recommendations:

- **Infants under age 18 months require virologic assays that directly detect HIV to diagnose HIV infection, since antibody assays cannot be used due to the persistence of maternal HIV antibody in this age group.**
- **Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at age 14–21 days; 1–2 months; and 4–6 months. Some experts also perform virologic testing at birth.**
- **Preferred virologic assays include HIV DNA PCR and HIV RNA assays.**
- **Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12–18 months to document seroreversion to HIV antibody negative status.**
- **In children age 18 months and older, HIV antibody assays can be used for diagnosis.**

CHOICE OF DIAGNOSTIC TEST (Updated October 26, 2006)

HIV infection can be definitively diagnosed through the use of virologic assays in most non-breastfed HIV-infected infants by age 1 month and in virtually all infected infants by age 4 months. 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 utilized *[1]*. A positive virologic test (i.e., detection of HIV by culture or DNA polymerase chain reaction [PCR] or RNA assays) indicates likely HIV infection and should be confirmed by a repeat virologic test on a second specimen as soon as possible after the first test result becomes available. 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 is less than that of other HIV virologic tests *[2-4]*.

HIV DNA PCR

HIV DNA PCR is a sensitive technique used to detect specific HIV viral sequences in integrated proviral HIV DNA in a patient's peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at <48 hours of age is less than 40%, but increases to over 90% by 2–4 weeks of age *[5-7]*. In a meta-analysis, 38% (90% confidence interval [CI] = 29%–46%) of infected children had positive HIV DNA PCR tests by age 48 hours *[8]*.

No substantial change in sensitivity during the first week of life was observed, but sensitivity increased rapidly during the second week, with 93% of infected children (90% CI = 76%–97%) testing positive by HIV DNA PCR by age 14 days. By age 28 days, HIV DNA PCR had 96% sensitivity and 99% specificity to identify HIV proviral DNA in PBMCs.

HIV RNA Assays

HIV 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. Several studies have demonstrated sensitivities of 25%–40% during the first weeks of life, increasing to 90%–100% by 2–3 months of age *[9-15]*. Similarly, specificity is comparable between the two tests, though the detection of low levels of HIV RNA (<10,000 copies/mL) may not be reproducible, and tests with low levels of HIV RNA should be repeated before they are interpreted as documenting the presence of HIV infection in an infant. Some clinicians choose to use an HIV RNA assay 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 guide treatment decisions. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (see HIV subtype section below). However, while HIV DNA PCR remains positive even in individuals receiving highly active antiretroviral therapy *[16]*, it is unknown whether sensitivity

of RNA assays might be affected by maternal antenatal treatment with combination antiretroviral drugs and/or infant antiretroviral prophylaxis.

HIV Viral Culture

HIV culture for the diagnosis of infection has a sensitivity that is similar to that of HIV DNA PCR *[17]*. However, HIV culture is more complex and expensive to perform than DNA PCR or RNA assays, is not generally available outside of research laboratories, and definitive results may not be available for 2–4 weeks.

ISSUES RELATED TO DIAGNOSIS OF NON-SUBTYPE B HIV INFECTION

(Updated October 26, 2006)

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 E in much of Southeast Asia *[18]*. Currently available HIV DNA PCR tests are less sensitive in the detection of non-subtype B HIV, and false-negative HIV DNA PCR assays have been reported in infants infected with non-subtype B HIV *[19-22]*. 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 to 4.4% of infants diagnosed between 1998–1999 *[23]*. Therefore, caution should be exercised in the interpretation of negative HIV DNA PCR test results in infants born to mothers who may have acquired infection with a non-subtype B virus.

Some of the currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection *[24-27]*, although even these assays may not detect some non-B subtypes, particularly the more uncommon group O HIV subtypes *[27,28]*. In cases of infants in whom non-subtype B perinatal exposure may be suspected and HIV DNA PCR is negative, repeat testing using one of the newer RNA assays shown to be more sensitive in the detection of non-subtype B HIV is recommended (e.g., the Amplicor HIV-1 Monitor 1.5 [Roche Molecular Systems, Pleasanton, CA], NucliSens HIV-1 QT [bioMerieux, Inc., Durham, NC], Versant Quantiplex HIV RNA 3.0 (bDNA) [Bayer Corporation, Tarrytown, NY]; AmpliPrep/TaqMan HIV-1 Test [Roche Diagnostics, Indianapolis, IN]; and Real Time HIV-1 Assay [Abbott Molecular Incorporated, Des Plaines, IL] assays). 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) *[27,29]*. In children with negative HIV DNA PCR and RNA assays but in whom non-subtype B infection continues to be suspected, the clinician should consult with an expert in pediatric HIV infection and the child should undergo close clinical monitoring and definitive HIV serologic testing at age 18 months.

TIMING OF DIAGNOSTIC TESTING IN INFANTS WITH KNOWN PERINATAL HIV EXPOSURE **(Updated February 28, 2008)**

Virologic diagnostic testing of the HIV-exposed infant should be performed at 14–21 days of age, at age 1–2 months, and at age 4–6 months. Some experts also perform virologic diagnostic testing at birth since as many as 30%–40% of infants with HIV infection can be identified by 48 hours of age.

HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples, regardless of age. A positive HIV antibody test with confirmatory Western blot (or IFA) at age ≥18 months confirms HIV infection *[1]*.

HIV infection can be *presumptively* excluded in non-breastfed infants with two or more negative virologic tests, with one test obtained at ≥14 days of age and one obtained at ≥1 month of age; or one negative virologic test result obtained at ≥2 months of age; or one negative HIV antibody test result obtained at ≥6 months of age *[30-32]*. Antibiotic prophylaxis against PCP 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. 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 and at 1 month of age, or if virologic testing is negative at or beyond 2 months of age. *Definitive* exclusion of HIV infection in a non-breastfed infant is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months. For both *presumptive* and *definitive* exclusion of HIV infection, the child

should have no other laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12–18 months to document seroreversion to HIV antibody negative status.

Virologic Testing at Birth (Optional)

Some experts will perform virologic testing at birth, because as many as 30%–40% of HIV-infected infants can be identified by 48 hours of age *[5,8]*. Because of concerns regarding potential contamination with maternal blood, blood samples from the umbilical cord should not be used for diagnostic evaluations. Working definitions have been proposed to differentiate between acquisition of HIV infection during the intrauterine and intrapartum periods. 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 *[33]*. 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 *[33,34]*. 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 age 7 days, these differences were no longer statistically significant after age 2 months *[35]*. HIV RNA copy number after the first month of life was more predictive of rapid disease progression than the time at which HIV culture tests were positive *[35]*.

Virologic Testing at 14–21 Days

The diagnostic sensitivity of virologic assays increases rapidly by age 2 weeks *[8]*, and early identification of infection would permit discontinuation of neonatal zidovudine chemoprophylaxis and further evaluation for initiation of combination antiretroviral therapy (see **When to Initiate Therapy in Antiretroviral-Naïve HIV-Infected Infants under Age 12 Months** and **Table 2**).

Virologic Testing at Age 1–2 Months

Infants with initially negative virologic tests should be retested at age 1–2 months. Most HIV-exposed neonates will receive 6 weeks of antiretroviral prophylaxis to prevent mother-to-child transmission. Although prophylactic antiretroviral therapy theoretically could affect the predictive value of HIV virologic testing in neonates, zidovudine monotherapy 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 *[12-15,36,37]*. Whether more intensive combination antiretroviral regimens used by HIV-infected pregnant women for treatment or prevention of transmission will affect virologic test sensitivity in their infants is being evaluated. The sensitivity of diagnostic testing will also need to be re-examined in HIV-exposed infants who receive more complex infant prophylaxis regimens for prevention of mother-to-child transmission. An infant with two negative virologic tests, one at ≥14 days and one at ≥1 month of age can be viewed as *presumptively* uninfected and would not need to initiate PCP prophylaxis, assuming the child has no laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection.

Virologic Testing at Age 4–6 Months

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

Antibody Testing at Age 6 Months or Older

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

Antibody Testing at Age 12–18 Months to Document Seroreversion

Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing serology after age 12 months to confirm that maternal HIV antibodies transferred to the infant *in utero* have disappeared, if there has not been previous confirmation of two negative antibody tests. If the child is still antibody-positive at age 12 months, then testing should be repeated between age 15–18 months *[38]*.

Antibody Testing Age 18 Months or Older

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

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Laboratory Monitoring of Pediatric HIV Infection

Working Group Recommendations:

- **In children under age 5 years, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group.**
- **CD4 percentage or count should be measured at the time of diagnosis of HIV infection and at least every 3–4 months thereafter.**
- **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.**
- **More frequent CD4 cell and plasma HIV RNA monitoring may be considered in infants less than age 6–12 months; in children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy.**
- **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.**
- **Optimally, the goal of antiretroviral therapy is to reduce plasma HIV RNA levels to below the limits of quantitation on ultrasensitive assays and to normalize immune status.**

IMMUNOLOGIC MONITORING IN CHILDREN (Updated February 28, 2008)

Clinicians interpreting CD4 count for children must consider age as a variable. CD4 count and percentage values in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults, and slowly decline to adult values by age 5 years *[1,2]*. In children under age 5 years, the absolute CD4 count tends to vary more with age within an individual child than does CD4 percentage. Therefore, in HIV-infected children under age 5 years, CD4 percentage is preferred for monitoring immune status, whereas absolute CD4 count can be used in older children *[3,4]*.

In HIV-infected children, as in infected adults, the CD4 count and percentage declines as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values (**Appendix Tables 1–3**). CD4 values should be obtained as soon as possible after a child has a positive test for HIV and every 3–4 months thereafter. Increased frequency of evaluations may be needed for children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy. Because young infants with HIV infection may have rapid disease progression, some experts monitor CD4 percentage more frequently (e.g., every 1–2 months) in untreated infants less than age 6–12 months. Because of the risk for rapid immunologic and clinical progression, initiation of antiretroviral treatment is recommended for all HIV-infected infants under age 12 months (see **When to Initiate Therapy in Antiretroviral Naïve Children**).

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

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 proportionately higher risks than older children for any given CD4 stratum. For example, comparing a 1-year-old child with CD4 percentage of 25% to a 5-year-old child with the same CD4 percentage, there is an approximate 4-fold increase in the risk of AIDS and 6-fold increase in the risk of death in the 1-year-old child (**Appendix 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 occurring at absolute CD4 levels more similar to young adults (**Appendix Figure 3**). In the HIV Pediatric Prognostic Marker Collaborative Study, there were no deaths among children age 5 years or older with CD4 count above 350 cells/mm^3, while in younger children there continued to be a significant risk of death even with a CD4 cell count above 500 cells/mm^3 (**Appendix Table 2**).

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

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

HIV RNA MONITORING IN CHILDREN (Updated February 28, 2008)

Viral burden in peripheral blood can be determined by using quantitative HIV RNA assays. During the period of primary infection in adults, HIV RNA copy number initially rises to high peak levels and then declines by as much as 2–3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6–12 months following acute infection *[6,7]*. In infected adults, the viral set point correlates with the subsequent risk of disease progression or death *[8,9]*. On the basis of data from studies in infected adults, recommendations for the use of HIV RNA copy number in deciding to initiate and change antiretroviral therapy have been developed for adults *[10]*. These recommendations also are applicable to infected adolescents.

The HIV RNA pattern in perinatally infected infants differs from that in infected adults. High HIV RNA copy numbers persist in infected children for prolonged periods *[11,12]*. 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 *[13]*. Additionally, in contrast to the adult pattern, after the first year of life, HIV RNA copy number slowly declines over the next few years *[13-16]*. This pattern probably reflects the lower efficiency of an immature, but developing, immune system in containing viral replication and possibly a greater number of HIV-susceptible cells.

High HIV RNA levels (i.e., >299,000 copies/mL) in infants age <12 months have been correlated with disease progression and death, but RNA levels overlap considerably in young infants who have rapid disease progression and those who do not *[12,13]*. High RNA levels (i.e., levels of >100,000 copies/mL) in older children have also been associated with high risk of disease progression and mortality, particularly if CD4 percentage is <15% (**Appendix Table 3**) *[15,16]*. The most robust data set available to elucidate the predictive value of plasma RNA for disease progression in children was assembled in the HIV Pediatric Prognostic Markers Collaborative Study discussed earlier (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 *[15,16]*, 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 (**Appendix Figures 4** and **5** and **Appendix Table 1**). At any given level of HIV RNA, infants under age 1 year 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 *[15]*. 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 *[11]*. 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 *[15-19]*.

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

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays **(Updated February 28, 2008)**

The use of HIV RNA assays for clinical purposes requires specific considerations *[20]*, which are discussed more completely elsewhere *[10]*. Several different methods can be used for quantitating HIV RNA, each with different levels 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 two-fold (0.3 $\log_{10}$) or more *[21-24]*.

There are currently five FDA-approved viral load assays:

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

The lower limit of detection for the assays differ (<40 copies/mL for Abbot 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). Because of the variability of assay techniques and quantitative HIV RNA measurements between the three assays, a single HIV RNA assay method should be used consistently for monitoring an individual patient. A key goal of therapy is to lower the viral load below the limit of detection of the chosen assay.

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 *[25,26]*. 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 viral subtypes prevalent in other parts of the world *[27-29]*. 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 3-fold (0.5 $\log_{10}$) in either direction over the course of a day or on different days *[10,19,24]*. 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 *[13-15]*. This decline is most rapid during the first 12–24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ per year; a slower decline continues until approximately age 4–5 years (average decline of 0.3 $\log_{10}$ per year).

This inherent biologic variability must be considered when interpreting changes in RNA copy number in children. Thus, only changes after repeated testing greater than 5-fold (0.7 $\log_{10}$) in infants age <2 years and greater than 3-fold (0.5 $\log_{10}$) in children age ≥2 years should be considered reflective of a biologically and clinically substantial change. To reduce the impact of assay variability in the clinical management of patients, 2 samples can be obtained at baseline and the average of the 2 values used for comparison with future tests.

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

GENERAL CONSIDERATIONS (Updated February 28, 2008)

Treatment of pediatric HIV infection in the United States has evolved since it began in the late 1980s. Prior to the availability of antiretroviral drugs for children, care focused on prevention and management of HIV-related complications and provision of palliative care. Initial studies of monotherapy in children in the early 1990s demonstrated significant clinical and immunologic benefit with treatment *[1-6]*; further research demonstrated that combination therapy (initially dual NRTI treatment) led to better clinical, immunologic, and virologic outcomes than monotherapy *[7-9]*. Currently, highly active combination regimens including at least 3 drugs are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children *[10-20]*. In the United States and United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of HAART *[13-15,21]*; significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period *[14,16,21,22]*.

The increased survival of HIV-infected children is associated with challenges in selecting successive new antiretroviral drug regimens. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be recognized in children *[23,24]*.

Antiretroviral drug-resistant virus can develop in both multi-drug experienced children and children who received initial regimens containing 1 or 2 drugs that incompletely suppressed viral replication. Additionally, drug resistance may be seen in antiretroviral-naïve children who have become infected with HIV despite maternal/infant antiretroviral prophylaxis *[25-27]*. Thus, decisions about when to start therapy and what drugs to choose in antiretroviral-naïve children and on how to best treat antiretroviral-experienced children remain complex, and 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. Separate sections will discuss treatment of antiretroviral-naïve children (when and what to start), when to change therapy, and treatment of antiretroviral-experienced children.

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

- Severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see pediatric clinical staging system for HIV, **Table 1**) *[28]*, level of CD4 cell immunosuppression, and magnitude of HIV plasma viremia;
- Availability of appropriate (and palatable) drug formulations and pharmacokinetic information on appropriate dosing in the child's age group;
- Potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the antiretroviral regimen;
- Effect of initial regimen choice on later therapeutic options;
- Presence of comorbidity that could affect drug choice, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease;
- Potential antiretroviral drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by the child; and
- The ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults,

with supporting pharmacokinetic and safety data from phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Working Group 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 (Updated October 26, 2006)

Current antiretroviral therapies do not eradicate HIV infection due to the long half-life of latently infected CD4 cells *[29-31]*; some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 versus 5–10 months, respectively) *[29]*. Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of antiretroviral therapy for HIV-infected children include:

- Reducing HIV-related mortality and morbidity;
- Restoring and/or preserving immune function;
- Maximally and durably suppressing viral replication;
- Minimizing drug-related toxicity;
- Maintaining normal physical growth and neurocognitive development; and
- Improving quality of life.

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

Use and selection of combination antiretroviral therapy: At present, the treatment of choice for HIV-infected children is at least 3 drugs, which include at least 2 classes of antiretroviral drugs. The Working Group has recommended several preferred and alternative regimens (see **What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children**). The most appropriate regimen for an individual child depends on multiple factors, including age of the child and availability of appropriate drug formulations; the potency, complexity, and toxicity of the regimen; the child and caregiver's ability to adhere to the regimen; the child's home situation; and the child's antiretroviral treatment history.

Drug sequencing and preservation of future treatment options: The choice of antiretroviral treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in antiretroviral drug regimens can rapidly exhaust treatment options, and should be avoided unless required (e.g., severe toxicity or intolerance or significant clinical, immunologic, or virologic progression). Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Currently, recommendations for initial therapy are to use 2 classes of drugs—2 NRTIs combined with either an NNRTI or PI—thereby sparing 3 classes of drugs for later use.

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

Table 1: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories* (Updated February 28, 2008)

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 **2** 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 aged >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 1: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories* (cont'd)
(Updated February 28, 2008)

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-Naïve Children (Table 2) (Updated February 28, 2008)

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

Recommendations for when to initiate therapy have been more aggressive in children than adults because HIV infection is primarily transmitted from mother to child, thereby allowing identification of the timing of infection in children; HIV disease progression in children is more rapid than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for young infants. As discussed in **Laboratory Monitoring of Pediatric HIV Infection**, CD4 count and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children younger than 12 months. Hence, recommendations for when to start therapy differ by age of the child. As discussed earlier, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, CD4 percentage and HIV RNA levels were both independently predictive of the risk of clinical progression or death in children older than 12 months, although CD4 percentage was a stronger predictor of risk than HIV RNA levels *[1]*. Based on data showing that surrogate-marker based risk of progression varies considerably by age but that CD4 count-associated risk of progression in children age 5 years or older is similar to young adults, the Working Group has moved to recommendations for 3 age bands for initiation of treatment: infants under age 12 months, children age 1 to <5 years, and children and adolescents age ≥5 years.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED INFANTS UNDER AGE 12 MONTHS

(Updated February 28, 2008)

Working Group Recommendations (Table 2):

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

While there is agreement among pediatric HIV experts that infected infants with clinical symptoms of HIV disease or with evidence of immune compromise should be treated, there remains controversy regarding treatment of asymptomatic infants with normal immunologic status. However, recent data from a South African clinical trial (Children with HIV Early Antiretroviral Therapy [CHER] study) of initiation of HAART in asymptomatic perinatally-infected children with normal CD4 percentage (CD4 >25%) prior to age 12 weeks compared to waiting to start HAART until the child meets clinical or immune criteria, demonstrated a 75% reduction in early mortality *[2]*. Most of the deaths in the children in the delayed arm occurred in the first 6 months after study entry. Because the risk of rapid progression is so high in young infants and based on the data from the CHER study, the Working Group recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage or viral load (**Table 2**). It is critical that issues associated with adherence are fully assessed and discussed with the HIV-infected infant's caregivers and addressed before therapy is initiated.

The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk of rapid disease progression. In early reports, approximately 20%–25% of HIV-infected children progressed to AIDS or death within the first year of life. In reports with follow-up through 1999, high rates of symptomatic disease progression continued to be observed in young infants, with development of AIDS or death in 15% of HIV-infected children by age 12 months, although children born between 1995–1999, where early treatment was recommended, were less likely to progress (5% developed AIDS or death by age 12 months) than those born earlier *[3]*. 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% severe immune suppression *[3]*. In the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger than older children at any given level of CD4 percentage, particularly for infants age <12 months *[4]*. Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections can occur in young infants with normal CD4 counts *[4]*.

Identification of HIV infection during the first few months of life permits clinicians to initiate antiretroviral therapy during the initial phases of primary infection. Data from a number of observational studies in the United Sates and Europe suggest that infants who receive early treatment with HAART are less likely to progress to AIDS or death than those who started later. Analyses from a prospective study of 360 HIV-infected children in the United States (Perinatal AIDS Collaborative Transmission Study [PACTS]) showed that infants who received early treatment with HAART (prior to age 2 years, with nearly half starting in the first year of life) were significantly less likely to progress to AIDS or death compared with those who received no therapy, adjusting for year of birth and maternal disease factors *[5]*. The French Perinatal Cohort reported a 70% reduction in the incidence of AIDS-associated events before age 24 months among infants born since 1996, and earlier initiation of HAART (before versus after age 6 months) appeared to be associated with a superior clinical outcome: there were no opportunistic infections or development of encephalopathy during the first 2 years of life among 40 infants who started HAART before age 6 months, whereas 6 of 43 infants who started HAART after age 6 months had 7 AIDS-defining events, 3 of which were encephalopathy *[6]*. The California Pediatric HIV Study Group and the Italian Register for Children both reported reduced disease progression to AIDS and improved survival with early initiation of HAART *[7-9]*. While very early initiation (before age 2 months) of mono/dual therapy resulted in decreased progression to AIDS compared to early initiation (age 3–4 months) of such therapy, the Italian Register did not find a difference in progression between children with very early versus early initiation of HAART; however, similar to the French Cohort, initiation of therapy at under age 6 months was superior to starting at >6 months *[6,9]*. In an analysis from the European Collaborative Study cohort, children who initiated potent therapy before age 5 months were more likely to achieve CD4 recovery (defined as 20% increase in CD4 z-score) than children initiating therapy at older ages *[10]*. Finally, as noted earlier, the randomized CHER clinical trial conducted in South Africa found that initiation of therapy at <12 weeks of age in asymptomatic infants with normal immune status resulted in lower mortality than waiting to initiate therapy in such children until they reached standard criteria for initiation of therapy *[2]*.

Several small studies have demonstrated that despite the very high levels of viral replication in perinatally-infected infants, early initiation of HAART can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, there has also been lack of detection of extra-chromosomal replication intermediates, suggesting near-complete control of viral replication. Some of these infants have become HIV seronegative and have lost HIV-specific immune responses. However, therapy is not curative: proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued *[11,12]*.

There are, however, potential problems with treatment of asymptomatic infants. The rates of virologic failure with therapy started early in life may be higher than when started later. In studies of early therapy, the proportion of infants with viral levels remaining below quantification after 12–24 months of therapy is lower than reported in older children and adults, ranging from 18%–62% *[13-19]*. Virologic suppression, however, may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults *[20]*. Incomplete viral suppression can lead to the development of drug resistance and compromise future

treatment options *[18]*. Possible reasons for the poor response in infants include very high viral loads in young infants, inadequate antiretroviral drug levels, and poor adherence due to the difficulties in administering complex regimens to infants. Information on appropriate drug dosing in infants under age 3–6 months is limited. Hepatic and renal functions are immature in the newborn, undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in antiretroviral dose requirements between young infants and older children. When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, antiretroviral drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. It is particularly critical that the importance of adherence to the treatment is fully discussed with the caregivers, and that potential problems are identified and resolved prior to initiation of therapy, even if this delays starting treatment. Frequent follow-up and continued assessment and support of adherence is 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 *[21,22]*. These concerns are particularly relevant because life-long administration of therapy may be necessary. Whether therapy begun in early infancy might be able to be stopped after a defined period of treatment (e.g., 1–2 years) that allowed the child to be protected during the period at greatest risk for HIV disease progression and mortality, with restarting of therapy when the child meets standard age-related criteria, is under assessment in clinical trials in South Africa and Kenya.

Surrogate markers such as CD4 count and HIV RNA levels are poor markers of disease progression in infants *[4]*. There are limited data on clinical indicators that may suggest an increased likelihood of rapid progression among asymptomatic infants that would allow an identification of a "high risk" group for whom early treatment is indicated. Some intriguing data suggest that the risk of disease progression during the first 2 years of life may be related to maternal clinical, immunologic, and virologic HIV disease status during pregnancy, with more rapid progression in infants born to women with more advanced HIV disease *[5]*.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED CHILDREN AGE 1 YEAR OR OLDER
(Updated February 28, 2008)

Working Group Recommendations (Table 2):

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

Because the risk of disease progression slows in children age ≥1 year, the option of deferring treatment can be considered for older children. It is clear that children with clinical AIDS or significant symptoms (clinical category C or B – **Table 1**) *[23]* are at high risk of disease progression and death; treatment is recommended by the Working Group for all such children, regardless of immunologic or virologic status. However, children age ≥1

year with mild clinical symptoms (clinical category A) or who are asymptomatic (clinical category N) are at lower risk of disease progression than those with more severe clinical symptoms *[24]*. It should also be noted that some clinical category B conditions—a single episode of serious bacterial infection or lymphoid interstitial pneumonitis—are less prognostic of the risk of disease progression, and consideration of CD4 count and viral load may be useful in determining the need for therapy in such children.

In adults, considerations related to initiation of antiretroviral therapy are based primarily on risk of disease progression as determined by baseline CD4 count (i.e., recommended if CD4 count is <350 cells/mm^3) *[25]*. Although there are not randomized clinical trial data to address the optimal time to initiate therapy in adults with a CD4 count >200 cell/mm^3, observational studies support initiation of treatment of adults with CD4 <350 cells/mm^3 *[25,26]*. In a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting HAART between 1995 and 2003, the risk of AIDS/death was significantly less in those who started HAART with CD4 count between 200–350 cells/mm^3 compared to those who started at <200 cells/mm^3 *[27]*.

In children, the prognostic significance of a specific CD4 percentage or count varies with age *[4,28]*. Data from pediatric studies also suggest the immune response to HAART children is better when treatment is initiated at higher CD4 percentage/count levels *[19,29]*. In data from the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count among children aged 1–4 years than among those 5 years or older (**Appendix Tables 1–2** and **Appendix Figures 1–2**). Data from the HIV Pediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children age 5 years or older, in whom the estimated risk of disease progression increases when the count falls below 350 cells/mm^3, similar to data in adults (**Appendix Table 2**) *[1,4]*. For children aged 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (**Appendix Table 1**). The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count *[4]*. Several studies have shown that older children with HIV RNA levels of ≥100,000 copies/mL are at high risk of mortality *[30,31]*; similar data have been reported in adults *[32]*. Similarly, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children older than age 1 year when HIV RNA levels were ≥100,000 copies/mL (**Appendix Table 1** and **Appendix Figures 4–5**) *[4]*. For example, the estimated 1-year risk of death was 2–3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared to 10,000 copies/mL, and 8–10 times higher if plasma RNA was >1,000,000 copies/mL.

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

For children who are age 5 years or older, initiation of antiretroviral therapy is recommended if they have AIDS or significant HIV-related symptoms (CDC clinical category C and clinical category B, except for the following category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 1**]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have CD4 <350 cells/mm^3, regardless of clinical symptoms or HIV RNA level. Treatment may be considered for children who are asymptomatic or have mild symptoms (clinical category N and A, or clinical category B disease due to a single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 1**]) with CD4 ≥350 cells/mm^3 if HIV RNA is >100,000 copies/mL. Antiretroviral therapy may be deferred for asymptomatic or mildly symptomatic children age ≥5 years who have CD4 ≥350 cells/mm^3 and who also have plasma HIV RNA levels <100,000 copies/mL.

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

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

Table 2: Indications for Initiation of Antiretroviral Therapy in Children Infected with Human Immunodeficiency Virus (HIV) (Updated February 28, 2008)

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

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat*
1–<5 years	• AIDS or significant HIV-related symptoms [1]	*Treat*
	• CD4 <25%, regardless of symptoms or HIV RNA level [2]	*Treat*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥25% *and* o HIV RNA ≥100,000 copies/mL	*Consider*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥25% *and* o HIV RNA <100,000 copies/mL	*Defer* [4]
≥5 years	• AIDS or significant HIV-related symptoms [1]	*Treat*
	• CD4 <350 cells/mm^3 [5]	*Treat*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA ≥100,000 copies/mL	*Consider*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA <100,000 copies/mL	*Defer* [4]

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

[2] The data supporting this recommendation are stronger for those with CD4 percentage <20% than for those with CD4 percentage between 20%–24%.

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

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

[5] The data supporting this recommendation are stronger for those with CD4 count <200 than for those with CD4 counts between 200–350 cells/mm^3.

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What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children (Tables 3–9)

Working Group Recommendations:

- **Combination therapy with at least 3 drugs, including either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus a dual nucleoside analogue reverse transcriptase inhibitor backbone, is recommended for initial treatment of HIV-infected children.**
- **The goal of therapy in treatment-naïve children is to reduce HIV RNA levels to below the level of detection (if possible, as determined using ultrasensitive assays) and to preserve immune function for as long as possible.**
- **Infants who are identified as HIV-infected during the first 6 weeks of life while receiving zidovudine chemoprophylaxis should have zidovudine discontinued and initiate treatment with combination therapy with at least 3 drugs (with drug choice based on results from antiretroviral drug resistance testing and treatment only initiated following assessment and counseling of the caregivers regarding adherence to therapy).**
- **Antiretroviral drug resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.**

GENERAL CONSIDERATIONS (Updated February 23, 2009)

As of February 2009, a total of 25 antiretroviral drugs have been approved for use in HIV-infected adults and adolescents; 17 of these have an approved pediatric treatment indication and 16 are available as a pediatric formulation or capsule size. Of the 25 antiretroviral drugs that have been approved, 3 are no longer being manufactured either because of the development of improved formulations (i.e., amprenavir replaced by fosamprenavir) or because of limited use (i.e., delavirdine and zalcitabine [ddC]). These drugs fall into several major classes: nucleoside analogue or nucleotide analogue reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs can be found in **Appendix B: Characteristics of Available Antiretroviral Drugs** for detailed information on drug interactions. For more detailed discussion of major classes of antiretroviral drugs and individual drugs for treatment of pediatric HIV infection, see **Supplement I: Pediatric Antiretroviral Drug Information**. It is likely that new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will become available over time, which will increase treatment options for children.

Aggressive combination antiretroviral therapy with at least 3 drugs from at least 2 classes of drugs is recommended for initial treatment of infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression. The goal of antiretroviral therapy is to maximally suppress viral replication, preferably to undetectable levels, for as long as possible, while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used.

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

Monotherapy with the currently available antiretroviral drugs is not recommended to treat HIV infection. Use of zidovudine as a single agent is appropriate only when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants who are confirmed as being HIV-infected while receiving zidovudine chemoprophylaxis should have zidovudine discontinued, and initiate treatment with combination therapy with at least 3 drugs, with the drug choice based on results from antiretroviral drug resistance testing and treatment only initiated following assessment and counseling of the caregivers regarding adherence to therapy.

Antiretroviral drug resistance testing is recommended prior to the initiation of therapy in all treatment-naïve children. Treatment-naïve children with perinatal HIV infection can acquire drug-resistant virus from their mothers (either because she was initially infected with drug-resistant virus or acquired drug resistance during treatment) or can develop resistance during the period of infant antiretroviral prophylaxis prior to diagnosis of HIV infection. Drug-resistant virus has been identified in 6%–16% of antiretroviral-naïve adults and 18% of horizontally infected adolescents with recent infection in United States and Europe *[1-5]*. Data are limited in children. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998–1999 and 19% of 42 infants born from 2000–2001 *[6,7];* history of maternal and infant antiretroviral prophylaxis was not significantly associated with the detection of resistance in the infant. Similarly, 24% of 21 infants initiating treatment (median age 9.7 weeks) were found to have mutations associated with drug resistance, most of which were not associated with maternal/infant prophylaxis regimens; resistant virus was found to be persistently archived in the resting CD4 cell reservoir *[8]*. Thus, the prevalence of infants infected with antiretroviral drug-resistant virus may be increasing and may not be predicted by the drug prophylaxis regimen received by the mother. Although definitive data are not yet available to demonstrate that resistance testing of antiretroviral-naïve children prior to initiation of therapy correlates with greater success of initial antiretroviral therapy, the prevalence of resistance in HIV-infected children is sufficiently high that based on expert opinion, the Working Group recommends resistance testing prior to initiation of therapy in all treatment-naïve children, similar to recommendations for HIV-infected adults *[9]*.

RECOMMENDED REGIMENS FOR INITIAL THERAPY OF ANTIRETROVIRAL-NAÏVE CHILDREN (TABLES 3 AND 4)

Criteria Used for Recommendations (Updated October 26, 2006)

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

Criteria used by the Working Group 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 palatability of formulations appropriate for pediatric use, including taste, 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.

The most extensive clinical trial data on initial therapy regimens in adults and children are available for 3 types of regimens based on drug class: NNRTI-based (2 NRTIs plus an NNRTI); PI-based (2 NRTIs plus a PI); and NRTI-based (3 NRTI drugs). NNRTI- or PI-based regimens are preferred for initial therapy; decisions about which type of regimen to choose should be individualized based on patient requirements. Each class-based regimen has advantages and disadvantages, which are delineated in more detail in the sections that follow and in **Tables 5–8**.

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

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use, and studies have been performed to demonstrate safety and surrogate marker efficacy in children; additional considerations are listed above.
- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared to 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 only for use in special circumstances, when preferred or alternative drugs cannot be used.
- ***Not Recommended:*** A list of drugs and drug combinations that are not recommended for initial therapy in children is shown in **Table 4**. These drugs and drug combinations are not recommended either because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism.
- ***Insufficient Data to Recommend:*** There are a number of drugs and drug combinations that are approved for use in adults that do not have pharmacokinetic or safety data available in children, or for which such data are too limited to make a recommendation for use for initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in the management of the treatment-experienced child (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

Preferred Regimens for Initial Therapy of Children (Table 3)

NNRTI-Based Regimens (1 NNRTI + 2 NRTI backbone) (Updated February 28, 2008)

Working Group Recommendations:

- **Preferred NNRTI:**
  - **Efavirenz in combination with 2 NRTIs for children age ≥3 years**
  - **Nevirapine in combination with 2 NRTIs for children age <3 years or who require a liquid formulation**
- **Alternative NNRTI:**
  - **Nevirapine in combination with 2 NRTIs (for children age ≥3 years)**

The Working Group does not recommend the following NNRTIs as initial therapy in children:

- **Etravirine, due to lack of pediatric formulation, lack of pediatric pharmacokinetic data, lack of efficacy or safety data in children, and lack of data in antiretroviral naïve patients**

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an approved pediatric indication. Nevirapine is available in a liquid formulation, while efavirenz is not, although a liquid formulation of efavirenz is under study. Advantages and disadvantages of different NNRTI drugs are delineated in **Table 6**. Use of NNRTIs as initial therapy preserves the PI class for future use, and less dyslipidemia and fat maldistribution have been reported with the NNRTI class than with the PI class. Additionally, there is a lower pill burden with these agents when compared to PI-based

regimens for children taking solid formulations. The major disadvantage of the current NNRTI drugs approved for use in children is that a single viral mutation can confer drug resistance, and cross-resistance develops between nevirapine and efavirenz. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all drugs in this class, but is most frequent with nevirapine, at least in HIV-infected adults.

Efavirenz, in combination with 2 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 comparative studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome, and rare but potentially life-threatening hepatitis *[10,11]*, nevirapine is recommended as an alternative NNRTI for initial treatment of antiretroviral-naïve children age ≥3 years. Nevirapine is the preferred NNRTI for initial therapy of children age <3 years or for children who require a liquid formulation.

Efavirenz as preferred NNRTI: In clinical trials in HIV-infected adults, a PI-sparing regimen of efavirenz in combination with zidovudine and lamivudine was associated with an excellent virologic response, with 70% of treated individuals having plasma HIV RNA <400 copies/mL at 48 weeks *[12]*. In randomized controlled trials in treatment-naïve adults, superior or similar virologic activity has been demonstrated in efavirenz-treated patients compared to individuals receiving PI- or triple NRTI-based regimens *[13-16]*. Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below) *[17-21]*. No comparative trials have been conducted in children.

Efavirenz has been studied in HIV-infected children in combination with 2 NRTIs or with an NRTI and a PI *[22-28]*. Results are comparable to those seen in adults. Although a pediatric formulation of efavirenz is under evaluation in the United States, at this time the drug is only available as a capsule or tablet. The appropriate dose of efavirenz for children age <3 years has not been determined, and it is therefore not recommended for this age group. Some clinicians would recommend opening the capsules and adding the contents to food or liquid for children age ≥3 years who cannot swallow pills; however, there are no pharmacokinetic data on use in this fashion.

The major limitations of efavirenz are central nervous system side effects in both children and adults; reported side effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. While in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after first initiating efavirenz. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in patients with higher levels of drug *[29-32]*. 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 *[22,23]*. Additionally, efavirenz is potentially teratogenic to the fetus if taken by a pregnant woman during the first trimester of pregnancy (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information). Unless adequate contraception can be assured, it is not recommended for initial therapy in adolescent females who are sexually active and may become pregnant.

Nevirapine as alternative NNRTI: Nevirapine has extensive clinical and safety experience in HIV-infected children, and has shown antiretroviral efficacy in a number of different combination regimens (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information) *[33]*. Nevirapine has been studied in HIV-infected children in combination with 2 NRTIs or with an NRTI and a PI *[34-36]*.

In a large adult trial (2NN trial), while virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine versus 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 to 5% on efavirenz) *[20]*. Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared to efavirenz-based regimens *[37]*. Additionally, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 count and in women, particularly women with CD4 >250 cells/mm^3 and men with CD4 >400 cells/mm^3. This may be less of an issue for pre-pubertal children. In the published literature, hepatic

toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults *[35,36,38]*. In an FDA review of 783 HIV-infected pediatric patients, there was only 1 case of hepatitis, which was reported in a 17-year-old; there was no evidence of a serious hepatic event associated with nevirapine use in any child prior to adolescence *[38]*. In contrast, skin and hypersensitivity reactions have been reported in children *[39]*. 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 *[40]*.

Because of the higher potential for toxicity, nevirapine-based regimens are considered as alternative rather than preferred in children age ≥3 years. Since appropriate dosing information for nevirapine in young children is available and there is a liquid formulation, nevirapine is the preferred NNRTI for children who are age <3 years or those who require a liquid formulation. Similar to recommendations in adults, nevirapine should not be used in post-pubertal adolescent girls with CD4 count >250/mm^3 due to the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk *[10]*.

PI-Based Regimens (1 or 2 PIs + 2 NRTI backbone) (Updated February 23, 2009)

Working Group Recommendations:

- **Preferred PI:**
  - **Lopinavir/ritonavir in combination with 2 NRTIs**
- **Alternative PI (listed alphabetically):**
  - **Atazanavir in combination with low dose ritonavir and 2 NRTIs (for children age ≥6 years)**
  - **Fosamprenavir in combination low dose ritonavir and 2 NRTIs (for children age ≥6 years)**
  - **Nelfinavir and 2 NRTIs (for children age ≥2 years)**
- **Use in special circumstances:**
  - **Atazanavir unboosted (for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir) in combination with 2 NRTIs (must be boosted with ritonavir if used with tenofovir)**
  - **Fosamprenavir unboosted (for children age ≥2 years) in combination with 2 NRTIs**

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

- **Tipranivir, darunavir, saquinavir, indinavir and other PIs not in the list above**
- **Dual (full dose) PIs**
- **Full dose ritonavir or use of ritonavir as the sole PI**
- **Unboosted atazanavir-containing regimens in children age <13 years and/or <39 kg**

Summary: PI-Based Regimens

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

metabolic complications), and availability of data in children (see **Table 7** for advantages and disadvantages and **Supplement I: Pediatric Antiretroviral Drug Information** for detailed pediatric information on each drug).

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs, and has been used in low doses combined with another PI as a "pharmacokinetic booster," increasing drug exposure by prolonging the second drug's half-life. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children over age 6 weeks *[41]* and atazanavir, fosamprenavir, and darunavir with low dose ritonavir in children age >6 years. The appropriate dosing of ritonavir-boosted PI regimens for other combinations is not known in children, and additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made and before such regimens can be recommended for initial therapy of treatment-naïve children. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia and drug-drug interactions.

The Working Group recommends coformulated lopinavir/ritonavir as the preferred PI for the treatment-naïve child based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, and availability of appropriate dosing information for children. However, data comparing the efficacy of lopinavir/ritonavir to other PIs are limited in adults and not available in children. Three PIs can be considered as alternative PIs for use in children: atazanavir in combination with low dose ritonavir for children age >6 years, fosamprenavir in combination with low dose ritonavir for children age >6 years, or nelfinavir for children age >2 years. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir alone in children age >2 years, atazanavir alone in adolescents age >13 years and >39 kg, or for older adolescents, saquinavir in combination with low dose ritonavir as discussed above. While good virologic and immunologic responses have been observed with indinavir-based regimens in adults, there is no liquid formulation and there has been a high rate of hematuria, sterile leukocyturia, and nephrolithiasis reported in pediatric patients with this drug *[42-45]*. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults *[42,45]*. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy. Additionally, newer PIs such as tipranavir and darunavir are not recommended for initial therapy at the present time due to limited data on use in treatment-naïve children, but may be considered for use in children with treatment failure.

Lopinavir/ritonavir as preferred PI: In clinical trials in adults, regimens containing lopinavir/ritonavir plus 2 NRTIs have been found to have very potent virologic activity in treatment-naïve patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had superior virologic efficacy to nelfinavir (plasma HIV RNA <400 copies/mL in 84% versus 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 to 45% of 43 nelfinavir-treated patients *[46,47]*. The rate of toxicity was similar between the groups. Lopinavir/ritonavir has been studied in both antiretroviral-naïve and -experienced children, and has demonstrated durable virologic activity and low toxicity *[48-51]*. In a study of 44 treatment-naïve children, 84% had plasma HIV RNA <400 copies/mL and 71% <50 copies/mL after 48 weeks of therapy (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information) *[49]*. In addition, dosing and efficacy data in infants under age 6 months is available *[50]*.

Atazanavir with low dose ritonavir as alternative PI (for children >6 years): Atazanavir is a once-daily PI that was approved for use in children >6 years of age in March 2008. It has equivalent efficacy to efavirenz-based HAART when given in combination with zidovudine and lamivudine in treatment-naïve adults *[52]*. When given with low dose ritonavir boosting, atazanavir achieves enhanced concentrations compared to the unboosted drug in adults and children >6 years of age *[53]* and in antiretroviral-naïve patients appears to be associated with fewer PI resistance mutations at virologic failure compared to atazanavir given without ritonavir boosting *[54]*. The main adverse effect associated with atazanavir/low dose ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher when using low-dose ritonavir boosting than atazanavir alone *[55]*.

Fosamprenavir with low dose ritonavir as alternative PI (for children ≥6 years): Fosamprenavir (the pro-drug of amprenavir) is now available in a pediatric liquid formulation and a tablet formulation. Amprenavir is no longer manufactured. In June 2007, fosamprenavir suspension was approved for use in pediatric patients ≥2 years of age. The approval was based on two open label studies in pediatric patients between 2 and 18 years of age *[56,57]*. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information). There is less pediatric experience with fosamprenavir than with lopinavir/ritonavir. 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, and therefore, this combination cannot be recommended in that age group. Once daily dosing of fosamprenavir is not recommended for pediatric patients.

Nelfinavir as alternative PI (for children ≥2 years): Nelfinavir is an alternative PI choice in combination with 2 NRTIs for initial treatment of children age ≥2 years. There is extensive pediatric experience with nelfinavir-based regimens in antiretroviral-naïve and -experienced children, with follow-up in children receiving the regimen for as long as 7 years *[58]*. The drug has been well tolerated, with diarrhea as the primary side effect, but virologic potency has been highly variable between studies, with reported rates of virologic suppression ranging from 26%–69% (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naïve pediatric patients *[59]*. In one such study, virologic response at week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% in children with therapeutic nelfinavir troughs (>0.8 mg/L) *[59]*. There is large interpatient variability in plasma concentrations in children, with lower levels in younger children *[50,60-65]*. The optimal dose of nelfinavir in younger children, particularly those age <2 years, has not been well defined, and higher doses of nelfinavir are required to achieve adequate drug levels in infants than in older children *[62]*. Pharmacokinetic parameters in adolescent patients have not been well studied, and doses higher than those recommended in adults may be required for some patients. These data, combined with data in adults showing lesser potency of nelfinavir compared to lopinavir/ritonavir, make nelfinavir an alternative choice for initial therapy of treatment-naïve children age ≥2 years, and not recommended for treatment of children age <2 years.

The pediatric formulation of nelfinavir is a powder that has a poor acceptance rate when mixed with food or formula, and the pharmacokinetics 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, although there are no pharmacokinetic data regarding use in this fashion.

In September 2007, the U.S. manufacturer, Pfizer, sent a letter to providers regarding the presence of ethyl methane sulfonate (EMS), a process-related impurity, in Viracept (nelfinavir mesylate), the product available in the United States, and recommending against starting nelfinavir in pediatric patients initiating antiretroviral therapy. As of March 31, 2008, all Viracept (nelfinavir) manufactured and released by Pfizer now meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients.

PIs for use in special circumstances:

Atazanavir without ritonavir boosting in children age ≥13 years: While unboosted atazanavir is approved for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir, data from the ongoing IMPAACT/PACTG 1020A study indicate that higher doses (on a mg/m^2 basis) are required to achieve adequate drug concentrations (see **Supplement I: Pediatric Antiretroviral Drug Information** for detailed information on dosing used in P1020A).

ACTG 5175 was a trial in antiretroviral-naïve adults that compared unboosted atazanavir plus the dual NRTI combination of enteric coated didanosine and emtricitabine given once daily, to efavirenz plus the dual NRTI zidovudine/lamivudine given twice daily or efavirenz plus the dual NRTI tenofovir/emtricitabine given once daily. At an interim analysis, the Data and Safety Monitoring Board for this trial recommended that subjects randomized to the atazanavir arm be unblinded and switched to an alternative regimen because of inferior virologic response

compared to the other two regimens *[66]*. If using unboosted atazanavir in treatment-naïve patients, clinicians should consider using an alternative dual NRTI combination to didanosine/emtricitabine. If these agents are to be used in combination, patients should be instructed to take them at least two hours apart, and to take atazanavir with food and didanosine on an empty stomach.

Fosamprenavir without ritonavir boosting in children age ≥2 years: Fosamprenavir used without ritonavir boosting in children 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.

Triple NRTI Regimens (Updated October 26, 2006)

Working Group Recommendations:

- **Use in special circumstances:**
  - **A 3 NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should only be used in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or adherence concerns).**

The Working Group does not recommend the following triple NRTI regimens as initial therapy in children due to inferior virologic potency:

- **Tenofovir + abacavir + lamivudine**
- **Tenofovir + didanosine + lamivudine**

Summary: Triple NRTI Regimens

Triple NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Because these triple NRTI regimens can be administered twice a day in children (adolescents who can receive adult doses can consider the triple combination of zidovudine/lamivudine/abacavir in a fixed-dose single tablet formulation [Trizivir]), they may also facilitate adherence. Data on the efficacy of triple NRTI regimens for treatment of antiretroviral-naïve children are limited; in small observational studies, response rates of 47%–50% have been reported *[67,68]*. In adult trials, these regimens have shown less potent virologic activity when compared to NNRTI- or PI-based regimens. Based on the results of these clinical trials and the potentially life-threatening hypersensitivity syndrome associated with abacavir use, the Working Group recommends that a 3 NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should only be used in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or concerns related to adherence).

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

Zidovudine + lamivudine + abacavir: In a randomized trial, the triple NRTI combination of zidovudine + lamivudine + abacavir was shown to reduce viral load to <400 copies/mL in 51% of treatment-naïve adults at 48 weeks of therapy, results equivalent to those of the PI-based comparison arm of zidovudine + lamivudine + indinavir *[69]*. 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 *[70]*. Additionally, a clinical trial (ACTG 5095) in antiretroviral-naïve adults that compared initial therapy with abacavir + zidovudine + lamivudine to efavirenz + zidovudine + lamivudine or efavirenz + abacavir + zidovudine + lamivudine found that the triple NRTI regimen was inferior to the efavirenz-based regimens, with a higher incidence of and an earlier time to virologic failure; after 48 weeks of therapy, 74% of adults receiving the triple NRTI regimen had HIV RNA <200 copies/mL, compared to 89% of patients receiving efavirenz-based regimens *[16,71]*.

Other triple NRTI regimens: Clinical trials in adults have also investigated triple NRTI regimens consisting of

stavudine + didanosine + lamivudine, stavudine + lamivudine + abacavir, and didanosine + stavudine + abacavir *[72-74]*. All of these regimens demonstrated inferior virologic response compared to their comparators. In addition, the M184V lamivudine drug resistance mutation was seen more frequently in patients treated with triple NRTI regimens containing lamivudine. Two additional triple NRTI regimens containing tenofovir have been studied in adults and are not recommended because of significantly higher rates of virologic failure. These two regimens are tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine *[75-77]*.

Selection of Dual NRTI Backbone as Part of Initial Combination Therapy (Updated February 28, 2008)

Working Group Recommendations:

- **Preferred 2 NRTI backbone combinations:**
  - **Abacavir + (lamivudine *or* emtricitabine)**
    - **HLA B*5701 genetic testing should be considered for HIV-infected children prior to initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA B*5701**
  - **Didanosine + emtricitabine**
  - **Zidovudine + (lamivudine *or* emtricitabine)**
  - **For post-pubertal or Tanner Stage 4 adolescents: tenofovir + (lamivudine *or* emtricitabine)**
- **Alternative 2 NRTI backbone combinations:**
  - **Zidovudine + (abacavir *or* didanosine)**
- **Use in special circumstances:**
  - **Stavudine + (lamivudine *or* emtricitabine)**

The Working Group does not recommend the following dual NRTI backbones for use in children:

- **Tenofovir-containing dual NRTI combinations in children in Tanner Stages 1–3 due to lack of pediatric dosing data and formulation and concerns related to bone toxicity**
- **Zidovudine + stavudine due to virologic antagonism**
- **Lamivudine + emtricitabine due to similar resistance pattern and no additive benefit**
- **Stavudine + didanosine due to toxicity (although not recommended for initial therapy, may be considered for use in antiretroviral-experienced children who require a change in therapy)**

Summary: Selection of Dual NRTI Backbone Regimen

Currently, 6 NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA-approved for use in children less than 13 years of age. Dual NRTI combinations form the "backbone" of HAART 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 *[28,58,65,78-80]*. Advantages and disadvantages of different dual NRTI backbone options are delineated in **Table 5**.

The preferred dual NRTI combinations for initial therapy in children consist of a primary NRTI (abacavir, didanosine, or zidovudine) combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine. Selection of the lamivudine- (or emtricitabine-) associated M184V mutation has been associated with increased susceptibility to zidovudine or tenofovir. This combination has extensive data on safety in children and is generally well tolerated. The major toxicities are bone

marrow suppression, manifested as macrocytic anemia and neutropenia. Minor toxicities include gastrointestinal toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few side effects. While there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine, and the Working Group felt it could be substituted for lamivudine as one component of a preferred dual regimen (i.e., emtricitabine in combination with abacavir, didanosine, or zidovudine). The advantages of emtricitabine are once daily administration, ability to be coadministered with didanosine, and its recent availability as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level cross resistance between both drugs, a modest decrease in susceptibility to abacavir and didanosine, and improved susceptibility to zidovudine, stavudine, and tenofovir *[81,82]*.

Abacavir in combination with lamivudine has been shown to be as or possibly more potent than zidovudine in combination with lamivudine in both children and adults *[83,84]*, but has the potential for abacavir-associated life-threatening hypersensitivity reactions in a small proportion of patients. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA B*5701 (see **Supplement I: Pediatric Antiretroviral Drug Information**); however the prevalence of HLA B*5701 is much lower in African American and Hispanic than Caucasian individuals in the United States (2%–2.5% compared to 8%) *[85]*; the majority of HIV-infected children in the United States are of minority race/ethnicity. Pre-treatment screening for HLA B*5701 prior to initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir hypersensitivity reaction in a study in HIV-infected adults *[86]*. Genetic screening for HLA B*5701 should be performed for HIV-infected children prior to initiating abacavir-based therapy. If testing is done, abacavir should not be given to children who test positive for HLA B*5701.

Didanosine in combination with emtricitabine is also a preferred dual NRTI combination because of the potential for once daily dosing. In a study in 37 treatment-naïve children aged 3 to 21 years, long-term virologic suppression was achieved with a once daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy *[28]*. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who feed frequently, and may decrease medication compliance in older children by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption with food *[87]*. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation *[88-91]*. Tenofovir in combination with lamivudine or emtricitabine is a preferred dual NRTI combination for use in adolescents in Tanner Stage 4 or who are post-puberty. The fixed-dose combinations of tenofovir + emtricitabine and tenofovir + emtricitabine + efavirenz are both administered as one pill once daily and may be particularly useful to improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine in viral efficacy *[92,93]*. A tenofovir-based dual NRTI combination has not been studied head-to-head with another dual NRTI backbone in a PI-based regimen but 48-week virologic efficacy of tenofovir + emtricitabine in combination with lopinavir/ritonavir was similar to that seen in trials with other dual NRTI backbones in treatment-naïve adults *[94]*. However, decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks in some, although not all, studies *[88-91]*. At this time there are insufficient data to recommend use of this drug for initial therapy in infected children in Tanner Stage 1–3, in whom the risk of bone toxicity may be greatest *[88,90]*. (see **Supplement I: Pediatric Antiretroviral Drug Information** for more detailed pediatric information). Renal toxicity has been reported in children as well as adults receiving tenofovir; in one single-center study, the rate of beta-2-microglobulinemia was higher in children receiving tenofovir than children receiving other antiretroviral agents (12/44 compared to 2/48, respectively), although creatinine clearance did not differ between groups *[95]*. Because of potential bone toxicity and renal toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment-naïve children. There are numerous drug-

drug interactions with tenofovir and other antiretroviral drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, complicating appropriate dosing of this drug.

Alternative dual NRTI combinations include zidovudine in combination with abacavir or didanosine. There is considerable experience with use of these dual NRTI regimens in children *[96]*. However, zidovudine + abacavir (as well as zidovudine + lamivudine) had lower rates of viral suppression and more toxicity leading to switching than did abacavir + lamivudine in one European pediatric study *[65,83]*.

The dual NRTI combination of stavudine in combination with lamivudine or emtricitabine is recommended for use in special circumstances because stavudine is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs *[97-99]*. For example, for 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 due to its lesser hematologic toxicity.

Certain dual NRTI drug combinations are not recommended. These include zidovudine + stavudine due to pharmacologic interactions that can result in potential virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the same single resistance mutation confers cross-resistance, so these drugs should not be used in combination. The dual NRTI combination of stavudine + didanosine is also not recommended for use as initial therapy. In small pediatric studies, stavudine + didanosine demonstrated virologic efficacy and was well tolerated *[78,80,100]*. However, in studies in adults, stavudine + didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine + lamivudine *[101,102]*; additionally, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy *[99,103]*.

Insufficient Data for Recommendation for Initial Therapy for Children (Updated February 23, 2009)

Working Group Recommendations:

Because of insufficient data for use as initial therapy, the following regimens should not be offered to children for initial therapy:

- **Low-dose ritonavir-boosted PI regimens, with exceptions of lopinavir/ritonavir (all ages), atazanavir/ritonavir in children age ≥6 years, and fosamprenavir/ritonavir in children age ≥6 years**
- **Dual (full dose) PI regimens**
- **Unboosted atazanavir-containing regimens in children age <13 years and/or <39 kg**
- **NRTI plus NNRTI plus PI**
- **Tenofovir-containing regimens in children in Tanner Stage 1–3**
- **Tipranavir- or darunavir-containing regimens**
- **Maraviroc-containing regimens**
- **Raltegravir-containing regimens**
- **Etravirine-containing regimens**
- **Enfuvirtide (T-20)-containing regimens**

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

Low-dose ritonavir-boosted PIs, with the exception of lopinavir/ritonavir (all ages), atazanavir/ritonavir in children age ≥6 years and fosamprenavir/ritonavir in children age ≥6 years: Three low-dose ritonavir-boosted PI combinations, lopinavir/ritonavir (available as a coformulated drug), atazanavir combined with low-dose ritonavir, and fosamprenavir combined with low-dose ritonavir, are recommended as preferred (lopinavir/ritonavir) and alternative (atazanavir or fosamprenavir with ritonavir) PI drugs for initial combination therapy in children. Low, nontherapeutic doses of ritonavir have been shown to act as a pharmacological "booster" to produce elevated therapeutic plasma concentrations of a second PI. Low-dose ritonavir boosting has been used with other PI drugs, including darunavir, indinavir, saquinavir, and tipranavir. However, data on use of these boosted PI combinations in children are too limited to recommend their use as a component of initial therapy in children. These combinations will have utility as components of secondary treatment regimens for children who have failed initial therapy.

Dual (full-dose) PI regimens: Due to the limited data on pharmacokinetics of full-dose dual PI combination regimens in children (e.g., saquinavir plus coformulated lopinavir/ritonavir or plus nelfinavir) *[104-106]*, these combinations are not recommended as initial therapy in children, although they may have utility as components of secondary regimens for children who have failed initial therapy.

Atazanavir without ritonavir boosting: Unboosted atazanavir-containing regimens are not recommended in children age <13 years and/or <39 kg due to lack of pediatric data on appropriate dosage.

Regimens containing 3 drug classes: There are insufficient data to recommend initial regimens containing agents from 3 drug classes (e.g., NRTI plus NNRTI plus PI). While efavirenz plus nelfinavir plus 1 or 2 NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naïve children and has the potential for inducing resistance to 3 drug classes, which could severely limit future treatment options *[23-25]*.

Tenofovir-containing regimens in children Tanner Stages 1-3: As noted in the **Selection of Dual NRTI Backbone as Part of Initial Combination Therapy** section, decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks and at this time there are insufficient data to recommend use of this drug for initial therapy in infected children in Tanner Stage 1–3, in whom the risk of bone toxicity may be greatest.

New agents without sufficient pediatric data for use as initial therapy (Tables 8 and 9): At this time there are several new agents that appear promising in adults but do not have sufficient pediatric pharmacokinetic and safety data to recommend their use as components of an initial therapeutic regimen in children. These include darunavir, maraviroc (the first of the CCR5 antagonists), raltegravir (the first of a new class of drugs, the integrase inhibitors), tenofovir, and etravirine (a new NNRTI). Raltegravir is being evaluated in children, but pharmacokinetic, safety, and efficacy data are not yet available and no pediatric formulation is commercially available. Etravirine is being evaluated in children but only limited data are available. Tipranavir boosted with ritonavir was approved (June 2008) by the FDA for use in treatment-experienced children age 2–18 years, but data are insufficient to address use as initial therapy. Darunavir combined with low-dose ritonavir boosting has been approved for antiretroviral-naïve and -experienced adults, and recently approved (December 2008) for children age ≥6 years. However, because pediatric approval of darunavir was based on one study in treatment-experienced children *[107]*, the currently available tablet dose formulations require a high pill burden to provide adequate darunavir dosing for children weighing under 40 kg, and several alternative options are available for initial treatment, the Working Group does not recommend darunavir for initial therapy in HIV-infected children, but notes that it, like tipranavir, has utility for use in treatment-experienced children.

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

What Not to Use: Antiretroviral Drug Regimens that Should Not be Offered at Any Time (Table 4) (Updated July 29, 2008)

Working Group Recommendations:

The following regimens should not be offered to children at any time:

- **Monotherapy**
- **Two NRTIs alone**
- **Certain 2 NRTI combinations as part of HAART regimen**
- **Two NRTIs + unboosted saquinavir**
- **Atazanavir + indinavir**
- **Tenofovir + didanosine + (lamivudine *or* emtricitabine)**
- **Tenofovir + abacavir + (lamivudine *or* emtricitabine)**

Several antiretroviral drugs and drug regimens are not recommended for use in therapy of children or adults. These are summarized below.

Monotherapy: Therapy with a single antiretroviral drug is not recommended because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drug being used and cross-resistance to other drugs within the same drug class. The exception is for preventive therapy of the newborn infant born to an HIV-infected mother, in which case 6 weeks of monotherapy with zidovudine is recommended for the infant (unless the infant is identified as infected, in which case zidovudine should be discontinued and standard triple therapy instituted) *[103]*.

Dual nucleoside regimens alone: Dual NRTI therapy alone is not recommended for initial therapy because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drugs being used and cross-resistance to other drugs within the same drug class. For children previously initiated on a dual NRTI regimen who have achieved viral suppression, it is reasonable to either continue on this therapy or to add a PI or NNRTI to the regimen. If a child is to stay on a 2 NRTI regimen, the plan should be to change to a 3 or more drug combination if viral rebound should occur (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

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

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

3 NRTI regimen of tenofovir + (didanosine or abacavir) + (lamivudine or emtricitabine): The triple NRTI combinations of tenofovir in combination with (didanosine or abacavir) plus (lamivudine or emtricitabine) have a high rate of early virologic non-response when used as initial therapy in treatment-naïve adults, and are not recommended *[75-77]*.

Table 3: Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children (Updated February 23, 2009)

A combination antiretroviral regimen in treatment-naïve children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. A 3-NRTI regimen consisting of zidovudine, abacavir, and lamivudine is recommended only if a PI- or NNRTI-regimen can't be used. Regimens should be individualized based on advantages and disadvantages of each combination (see **Tables 6, 7, 8**).

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Preferred Regimen:	Children ≥3 years old: Two NRTIs ***plus*** efavirenz [1]
	Children <3 years old or who can't swallow capsules: Two NRTIs ***plus*** nevirapine[1]
Alternative:	Two NRTIs ***plus*** nevirapine[1] (children ≥3 years old)
Protease Inhibitor-Based Regimens	
Preferred Regimen:	Two NRTIs ***plus*** lopinavir/ritonavir
Alternative (listed alphabetically):	Two NRTIs ***plus*** atazanavir ***plus*** low dose ritonavir (children ≥6 years old)
	Two NRTIs ***plus*** fosamprenavir ***plus*** low dose ritonavir (children ≥6 years old)
	Two NRTIs ***plus*** nelfinavir (children ≥2 years old)
Use in Special Circumstances	
	Two NRTIs ***plus*** atazanavir unboosted (for treatment-naïve adolescents ≥13 years of age and >39 kg)
	Two NRTIs ***plus*** fosamprenavir unboosted (children ≥2 years old)
	Zidovudine ***plus*** lamivudine ***plus*** abacavir
2-NRTI Backbone Options (for use in combination with additional drugs) (alphabetical ordering)	
Preferred	Abacavir ***plus*** (lamivudine ***or*** emtricitabine)
	Didanosine ***plus*** emtricitabine
	Tenofovir ***plus*** (lamivudine ***or*** emtricitabine) (for Tanner Stage 4 or post-pubertal adolescents only)
	Zidovudine ***plus*** (lamivudine ***or*** emtricitabine)
Alternative	Abacavir ***plus*** zidovudine
	Zidovudine ***plus*** didanosine
Use in Special Circumstances	Stavudine ***plus*** (lamivudine ***or*** emtricitabine)

Table 3: Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children (cont'd)
(Updated February 23, 2009)

Insufficient Data to Recommend for Initial Therapy	
	Low-dose ritonavir-boosted PI regimens, with exceptions of lopinavir/ritonavir (any age), atazanavir/ritonavir in children ≥6 years old, and fosamprenavir/ritonavir in children ≥6 years old[2]
	Dual (full dose) PI regimens
	NRTI ***plus*** NNRTI ***plus*** PI
	Tenofovir-containing regimens in children in Tanner Stage 1–3
	Unboosted atazanavir-containing regimens in children <13 years of age and/or <39 kg
	Tipranavir- or darunavir-containing regimens
	Etravirine-containing regimens
	Enfuvirtide (T-20)-containing regimens
	Maraviroc-containing regimens
	Raltegravir-containing regimens

[1] Efavirenz is currently available only in capsule form and should only be used in children ≥3 years old with weight ≥10 kg; nevirapine would be the preferred NNRTI for children age <3 years old or who require a liquid formulation. Unless adequate contraception can be assured, efavirenz-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

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

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor
ABC: abacavir; ddI: didanosine; FTC: emtricitabine; 3TC: lamivudine; d4T: stavudine; ZDV: zidovudine

Table 4: Antiretroviral Regimens or Components that Should Not Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children (Updated July 29, 2008)

	Rationale	Exceptions
Antiretroviral regimens not recommended		
Monotherapy	• Rapid development of resistance • Inferior antiviral activity compared to combination with ≥3 antiretroviral drugs	• HIV-exposed infants (with negative viral testing) during 6 week period of prophylaxis to prevent perinatal transmission
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared to combination with ≥3 antiretroviral drugs	• Not recommended for initial therapy; for patients currently on this treatment, some clinicians may opt to continue if virologic goals are achieved
Tenofovir ***plus*** 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 exception
Tenofovir ***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 exception
Antiretroviral components not recommended as part of an antiretroviral regimen		
Atazanavir ***plus*** indinavir	• Potential additive hyperbilirubinemia	• No exception
Dual NRTI combinations:		
• 3TC ***plus*** FTC	• Similar resistance profile and no additive benefit	• No exception
• d4T ***plus*** ZDV	• Antagonistic effect on HIV	• No exception
• d4T ***plus*** ddI	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis	• May be considered for use in antiretroviral-experienced children who require therapy change
Efavirenz in first trimester of pregnancy or sexually active adolescent girls of childbearing potential	• Potential for teratogenicity	• When no other antiretroviral option is available and potential benefits outweigh risks
Nevirapine initiation in adolescent girls with CD4 >250 cells/mm^3 or adolescent boys with CD4 >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs the risk
Unboosted saquinavir	• Poor oral bioavailablity • Inferior virologic activity compared to other protease inhibitors	• No exception

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 5: Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (Updated February 28, 2008)

	Advantages	Disadvantages
Preferred Combinations		
ABC ***plus*** 3TC ***or*** FTC	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients	• Potential for ABC hypersensitivity reaction; consider HLA-B*5701 screening prior to initiation of ABC treatment
ddI ***plus*** 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 (but can be coadministered with FTC) • Limited pediatric experience using delayed-release capsules in younger children • Pancreatitis, neurotoxicity with ddI
ZDV ***plus*** 3TC ***or*** FTC	• Extensive pediatric experience • Coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • FTC available as a palatable liquid formulation administered once daily	• Bone marrow suppression with ZDV
Tenofovir ***plus*** 3TC ***or*** FTC for Tanner Stage 4 or post-pubertal adolescents only	• Resistance slow to develop • Once daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in post-pubertal children • Tenofovir and FTC are coformulated as single pill for older/larger patients	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/RTV, ATV, and TPV complicating appropriate dosing
Alternate Combinations		
ABC ***plus*** ZDV	• Palatable liquid formulations • Can give with food	• Potential for ABC hypersensitivity reaction; consider HLA-B*5701 screening prior to initiation of ABC treatment • Bone marrow suppression 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 dosing	• Bone marrow suppression with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation less palatable than 3TC or FTC liquid formulation • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food) – some experts give ddI without regard to food in infants or when compliance is an issue

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NtRTI: Nucleotide analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 5: Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 28, 2008)

	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
Insufficient Data to Make Recommendation		
Tenofovir-containing regimens in children in Tanner Stages 1–3	• Resistance slow to develop • Once daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity; bone toxicity appears to be more frequent in younger children • Numerous drug-drug interactions with other ARV agents including ddI, LPV/RTV, ATV, and TPV complicating appropriate dosing
Not Recommended		
ZDV ***plus*** d4T	• None	• Pharmacologic and antiviral antagonism
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 antiretroviral-experienced children who require a change in therapy	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NtRTI: Nucleotide analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 6: Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

(Updated February 28, 2008)

	Advantages	Disadvantages
General Issues		
NNRTI-Based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than protease inhibitors • Protease inhibitor-sparing • Lower pill burden than protease inhibitors for those taking solid formulation; easier to use and adhere to than protease inhibitor-based regimens	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross-resistance between EFV and NVP • Rare but serious and potentially life-threatening cases of skin rash, including Stevens-Johnson Syndrome, and hepatic toxicity with all NNRTIs (but highest with nevirapine) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
Preferred		
Efavirenz (for children ≥3 years old and who can take capsules)	• Potent antiretroviral activity • Once daily administration • Can give with food (but avoid high fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children <3 years old • Teratogenic in primates; use with caution in adolescent females of childbearing age
Alternative		
Nevirapine (alternative NNRTI for children ≥3 years old; strongly recommended NNRTI for children <3 years old or who can't swallow capsules)	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence rash/ hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Need for initiating therapy with a lower dose and increasing in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity
Insufficient Data to Recommend		
Etravirine	• Three or more baseline NNRTI mutations result in a decreased virologic response • Patients with a history of NNRTI-related rash do not appear to be at increased risk of etravirine-related rash	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naïve patients • Multiple drug interactions with PI's and other medications

NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (Updated February 23, 2009)

	Advantages	Disadvantages
General Issues		
Protease Inhibitor-Based Regimens	**Protease Class Advantages:** • NNRTI-sparing • Clinical, virologic and immunologic efficacy well-documented • Resistance to protease inhibitors requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**Protease Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for those taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
Lopinavir/ ritonavir	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with food or snack	• Poor palatability of liquid (bitter taste), although better than ritonavir alone • Food effect (liquid should be administered with food) • Ritonavir component associated with large number of drug interactions (see ritonavir)
Alternative		
Atazanavir in combination with low dose ritonavir in children age ≥6 years	• Once daily dosing • Atazanavir has less effect on triglyceride and total cholesterol levels than other Ps (but ritonavir boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)
Fosamprenavir in combination with low dose ritonavir in children age ≥6 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • Ritonavir component associated with large number of drug interactions (see ritonavir)
Nelfinavir in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625mg) twice a day regimen has a reduced pill burden compared to 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 three times daily dosing for younger children • Adolescents may require higher doses than adults

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 23, 2009)

	Advantages	Disadvantages
Use in Special Circumstances		
Fosamprenavir (unboosted) in children age ≥2 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • May require boosted regimen to achieve adequate plasma concentrations but pharmacokinetic data to define appropriate dosing not yet available
Atazanavir (unboosted) in treatment-naïve adolescents age ≥13 years and >39 kg, who are unable to tolerate ritonavir	• Once daily dosing • Less effect on triglyceride and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require RTV boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Insufficient Data to Recommend		
Darunavir	• Effective in PI-experienced children when given with low-dose ritonavir boosting	• Pediatric data limited to antiretroviral-experienced children • Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations • Contains sulfa moiety; potential for cross-sensitivity between darunavir and other drugs in sulfonamide class is unknown.
Tipranavir	• Effective in PI-experienced children and adults when given with low-dose ritonavir boosting • Liquid formulation	• Limited data in treatment-naïve patients • Food effect (should be administered with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations
Not Recommended		
Atazanavir (unboosted) in children <13 years and/or <39 kg	• Once daily dosing (≥13 years) • Less effect on triglyceride and total cholesterol levels than other PIs	• Drug levels low if used without ritonavir boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require RTV boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Indinavir (unboosted)	• May be considered for use as component of a regimen in combination with low-dose ritonavir in post-pubertal 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 pharmacokinetic data
Ritonavir (full dose)	• Liquid formulation • Can be given with food	• Poor palatability of liquid (bitter taste) • Gastrointestinal intolerance • Food effect (should be administered with food) • Largest number drug interactions (most potent inhibitor of CYP3A4)

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 23, 2009)

	Advantages	Disadvantages
Not Recommended (cont'd)		
Saquinavir (unboosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric pharmacokinetic data; will require boosting with another PI (e.g., ritonavir) to achieve adequate concentrations • No liquid formulation • High pill burden • Must be taken with food • Photosensitivity reactions can occur

Table 8: Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens (Updated February 28, 2008)

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with enfuvirtide • CCR5 inhibitors ineffective against CXCR4 virus or mixed CCR5 and CXCR4 viral populations or dual tropic virus
Use in Special Circumstances		
Enfuvirtide	• Susceptibility of HIV to a new class of ARVs • Route of administration assure adequate drug levels	• Twice daily subcutaneous injections • 98%–100% incidence of local injection site reactions
Insufficient Data to Recommend		
Maraviroc	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation

Table 9: Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens (Updated February 28, 2008)

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

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Monitoring of Children on Antiretroviral Therapy (Updated February 28, 2008)

Working Group Recommendations:

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

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

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

Subsequently, children taking antiretroviral medication should have assessments of adherence, toxicity, and efficacy at least every 3–4 months. **Table 10** provides one proposed monitoring schema, which will require adjustment based on the specific therapy the child is receiving. Assessments should include basic hematology, chemistry, CD4 count/percentage, and HIV viral load. Monitoring of drug toxicities should be tailored to the particular medications the child is taking; for example, periodic monitoring of pancreatic enzymes may be desirable in children receiving didanosine, or of serum glucose and lipids in patients receiving PIs. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (e.g., evaluation of serum lactate in a child receiving NRTI drugs who develops symptoms suspicious for lactic acidosis) performed more frequently until the toxicity resolves. For further details of adverse effects associated with particular antiretroviral medications, please see **Supplement III: Adverse Drug Effects**.

Table 10: Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy (Updated February 28, 2008)

Time after Starting Therapy	Toxicity Monitoring[1]	Adherence and Efficacy Monitoring
Baseline (prior to initiation of therapy)	Clinical history, complete blood count and differential, chemistries[3]	$CD4^+$ cell count/percentage, HIV RNA
1-2 weeks[2]	Clinical history	Adherence screen
4-8 weeks	Clinical history, complete blood count and differential, chemistries[3]	Adherence screen, $CD4^+$ cell count/percentage, HIV RNA
Every 3-4 months	Clinical history, complete blood count and differential, chemistries[3]	Adherence screen, $CD4^+$ cell count/percentage, HIV RNA
Every 6-12 months	Lipid Panel	

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

[2] Children starting a new antiretroviral regimen should be evaluated in person or by a phone call within 1 to 2 weeks of starting medication to screen for clinical side effects and to assure that they are taking medication properly; 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.

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

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated October 26, 2006)

Working Group Recommendations:

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

BACKGROUND

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

DOSING OF ANTIRETROVIRAL THERAPY FOR HIV-INFECTED ADOLESCENTS

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

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

ADOLESCENT CONTRACEPTION, PREGNANCY, AND ANTIRETROVIRAL THERAPY

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

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

Contraceptive-Antiretroviral Drug Interactions

Several PI and NNRTI drugs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see **Tables 15a-b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***). These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered in cases in which there are documented interactions. It is unknown whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot methoxyprogesterone acetate [DMPA]) would be compromised, as these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered among women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional side effects, and no clinically significant changes in antiretroviral drug levels *[6]*. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Adolescents who express a desire to become pregnant should be referred for pre-conception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy (see **Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions for Prevention of Perinatal HIV-1 Transmission in the United States***)* *[7]*.

Pregnant Adolescents

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for non-pregnant adults or adolescents. Details regarding choice of antiretroviral regimen in pregnant HIV-infected women, including adolescents, are provided in the **Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions for Prevention of Perinatal HIV-1 Transmission in the United States** *[7]*.

TRANSITION OF ADOLESCENTS INTO ADULT HIV CARE SETTINGS

Facilitating a smooth transition for adolescents with any chronic health condition from the child or adolescent health system to one devoted to the care of adults may be difficult, and is especially so for those 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” *[8]*. HIV care models for children and perinatally infected adolescents tend to be family-centered, with input from members of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have a long-standing relationship with patients and their families, and the care is rendered in discreet, more intimate settings. Although expert care is also rendered in the adult HIV care medical model, the adolescent may feel unfamiliar with the more individual-centered, busier clinics typical of adult medical providers, who themselves may not have as long-standing a relationship with the adolescent. Providing support and guidance to the adolescent and to the adult medical care provider as to what is expected from each may be helpful. Some general guidelines about

transitional plans and who might best benefit from them are available *[9,10]*. Pediatric and adolescent programs may benefit from the establishment of formal programs to introduce adolescents to the adult care setting.

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated October 26, 2006)

Working Group Recommendations:

- **Strategies to maximize adherence should be discussed prior to initiation of antiretroviral therapy and again at the time of changing regimens.**
- **Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence.**
- **Multiple methods of determining adherence to antiretroviral therapy should be used simultaneously (e.g., quantitative self-report, pharmacy refill checks, pill counts).**
- **A non-judgmental attitude and trusting relationship will foster open communication and facilitate assessment of adherence.**

BACKGROUND

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

Evidence indicates that adherence problems occur frequently in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to their regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), antiretroviral regimens, and study characteristics *[2,3,8-11]*. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial characteristics of the child and parent, have been associated with adherence, but no clear predictors of either good or poor adherence in children have been consistently identified *[6,10,11]*. These findngs illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence education, support, and assessment integral components of care.

SPECIFIC ADHERENCE ISSUES IN CHILDREN

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient factors, and characteristics of health care providers. Limited availability of palatable formulations for young children is especially problematic *[7,12]*. Furthermore, infants and young children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multi-drug regimen requires evaluation of the caregivers and their environments as well as the ability and willingness of the child to take the drug. Some caregivers may place too much responsibility on older children for managing medications before they are developmentally able to take on such tasks. Many other barriers to adherence exist for children with HIV infection. For example, unwillingness of the caregivers to disclose the child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions in their home neighborhoods, hiding or relabeling medications to maintain secrecy within the household, reduction of social support, and a tendency to skip doses when the parent is away from the home or when the child is at school.

SPECIFIC ADHERENCE ISSUES FOR ADOLESCENTS

HIV-infected adolescents also face specific adherence challenges *[6,13,14]*. Several studies have identified pill burden as well as lifestyle issues (not carrying medication, change in schedule) as barriers to complete adherence *[6,13]*. Denial and fear of their HIV infection is common, especially in recently diagnosed youth; this may lead to

refusal to initiate or continue antiretroviral therapy. Distrust of the medical establishment, misinformation about HIV, and a lack of knowledge about the availability and effectiveness of antiretroviral treatments can all be barriers to linking adolescents to care and maintaining successful antiretroviral therapy. Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they may have long histories of inadequate adherence. Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, may have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness due to a lack of familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease stage all correlate with nonadherence *[14]*. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties face adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and those who are homeless and have no place to store medicine. Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to antiretroviral treatment have not been rigorously evaluated in adolescents. Preliminary data suggest that interventions based on the "stages of change" model, which assesses adolescents' readiness to adhere to medications, may facilitate adherence *[15]*. An intervention approach involving both family and peers to increase adherence in HIV positive youth appears to be effective *[16]*. In clinical practice, the use of reminder systems, such as beepers and alarm devices, are well accepted by some youth. Small, discreet pillboxes in which to store medications in an organized fashion may be useful *[17]*.

ADHERENCE ASSESSMENT AND MONITORING

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

Adherence is difficult to assess accurately; different methods of assessment have been shown to yield different results, and each approach has limitations *[18]*. Both caregivers and health care providers often overestimate adherence. Regular monitoring is key to early identification of problems and can reinforce the importance of taking medications as prescribed.

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 multi-drug-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. Targeted questions about stress, pill burden, and daily routine are recommended *[6,11,18]*. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports *[19]*. Electronic monitoring devices, such as Medication Event Monitoring Systems (MEMS) caps, which record opening of medication bottles on a computer chip in the cap *[20]*, have been shown to be useful tools to measure adherence in some settings *[19,21]*. Home visits can play an important role in assessing adherence, and in some cases, suspected nonadherence is confirmed only when dramatic clinical responses to antiretroviral therapy occur during hospitalizations or in other supervised settings *[22-24]*. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence *[25]*.

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 non-judgmental attitude and trusting relationship fosters open communication and facilitates assessment. It is often helpful to ask both older children and caregivers about missed doses and problems. There can be significant discrepancies between parent and child reports. Therefore, clinical judgment is required to best interpret adherence information obtained from multiple sources *[26]*.

STRATEGIES TO IMPROVE AND SUPPORT ADHERENCE

Intensive follow-up is required, particularly during the critical first few months after therapy is started; patients should be seen frequently to assess adherence and determine the need for strategies to improve and support adherence. Strategies include the 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 tooth-brushing), 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 *[27-29]*. Although quite labor-intensive, programs designed to administer directly observed HAART to adults in either the clinic or at home have demonstrated successful results in both the United States and in international, resource-poor settings *[30-33]*. **Table 11** summarizes some of the strategies that can be used to support and improve adherence to antiretroviral medications.

Regimen-Related Strategies

Highly active antiretroviral regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects. 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. When nonadherence is related to poor palatability of a liquid formulation or crushed pills, the offending taste may be masked by a small amount of flavoring syrups or food, as long as the medication is not one with contraindications to simultaneous administration of food (see **Appendix B: Characteristics of Available Antiretroviral Drugs**), or the child may be taught to swallow pills in order to overcome medication aversion *[34]*.

Child/Family-Related Strategies

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

A number of behavioral tools can be used to integrate medication-taking 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 *[35-37]*. Availability of mental health services and treatment of mental health disorders may also facilitate adherence to complex antiretroviral regimens. For nonadherent children who are at risk of disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered *[38]*. Home nursing interventions may also be beneficial where adequate resources are available *[39]*. Directly observed dosing of antiretroviral medications has been implemented in adults with promising results *[30-33,40]*, and such an approach has been implemented in some pediatric HIV programs, using home nursing services as well as daily medication administration in the clinic setting.

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. 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. Several online resources are available to assist HIV health care providers to become knowledgeable about adherence, the factors affecting it, and strategies to support and improve adherence in children, youth, and adults:

- **http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL_AdherenceSup.pdf**
- **http://www.hivguidelines.org/public_html/center/best-practices/treatment_adherence/pdf/treat_adherence_full.pdf**
- **http://www.hivguidelines.org/public_html/center/clinical-guidelines/ped_adolescent_hiv_guidelines/html/peds_supportive_care/pdf/supportive_care.pdf**
- **http://www.positivelife.net**

Table 11: Strategies to Improve Adherence with Antiretroviral Medications

(Updated October 26, 2006)

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on need for treatment and adherence. • Identify depression, low self-esteem, drug use or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat prior to starting antiretroviral drugs, if possible. • Identify family, friends, health team members, or others who can help with adherence support. • Educate patient and family about the critical role of adherence in therapy outcome. • Specify the adherence target: 95% of prescribed doses. • Educate patient and family about the relationship between partial adherence and resistance. • Educate patient and family about resistance and constraint of later choices of antiretroviral drug; i.e., explain that while 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.
Follow-up Intervention Strategies
• Monitor adherence at each visit, and in between visits by telephone or letter as needed. • Provide ongoing support, encouragement, and understanding of the difficulties of the demands of attaining >95% adherence with medication doses. • Use patient education aids including pictures, calendars, stickers. • Use pill boxes, reminders, alarms, pagers, timers. • Provide nurse, social worker, or other practitioner adherence clinic visits or telephone calls. • Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence. • Provide pharmacist-based adherence support • Consider gastrostomy tube use in selected circumstances. • Consider a brief period of hospitalization for selected circumstances of apparent virologic failure, to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy. • Consider directly observed therapy at home, in the clinic, or during a brief inpatient hospitalization.

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Management of Medication Toxicity or Intolerance (Updated October 26, 2006)

Working Group Recommendations:

- **If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately. Once the symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of another antiretroviral drug for the responsible drug.**
- **Children with moderate medication toxicity should continue on antiretroviral therapy when possible while an assessment is done to identify and substitute for the offending agent.**
- **Children with mild toxicity can be treated symptomatically, and do not require drug discontinuation or change in drug therapy.**
- **When changing therapy because of toxicity or intolerance to a specific drug, changing a single drug in a multi-drug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen.**
- **The toxicity and the medication thought to be responsible for it should be documented in the medical record and the caregiver and patient made aware of the drug-related toxicity to assist in making future medication choices if care is transferred.**
- **Dose reduction is not a recommended option in the setting of antiretroviral toxicity except in the instance when therapeutic drug monitoring has been performed and indicated a drug concentration above the normal therapeutic range.**

Side effects of antiretroviral agents or intolerance to them occur with moderate frequency and should prompt a re-evaluation of the antiretroviral regimen. Drug-related toxicity may be acute, occurring soon after a drug has been administered; subacute, occurring within 1–2 days of administration; or late, occurring after prolonged drug administration. Such adverse events may vary in severity from mild to severe and life-threatening.

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

Experience with antiretroviral drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain antiretroviral drugs or drug classes, including:

- hematological adverse events associated with drug-induced bone marrow suppression, most common with zidovudine;
- mitochondrial dysfunction, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy;
- lipodystrophy and metabolic abnormalities, primarily seen with stavudine and the PI drugs, and to a lesser degree with certain other NRTI drugs (abnormalities include fat maldistribution and body habitus changes; hyperlipidemia; hyperglycemia, insulin resistance, and diabetes mellitus; and osteopenia, osteoporosis, and osteonecrosis); and
- allergic reactions such as skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs, such as abacavir.

Detailed information about specific adverse drug effects and their management can be found in **Supplement III: Adverse Effects**.

In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution; symptomatic treatment may be given, such as antihistamines for a mild rash. Some moderate toxicities may require the substitution of an antiretroviral drug associated with toxicity with a drug in the same drug class but with a different toxicity profile, but do not require discontinuation of all therapy. The response to a medication-related toxicity should be discussed by the physician, patient, and caregiver, and should take into account the severity of toxicity, the relative need for viral suppression, and the available antiretroviral options. Severe, life-threatening toxicity requires discontinuation of all antiretroviral drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity), and 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 adverse effects from antiretroviral therapy and it is unclear which medication is responsible, every attempt should be made to identify the agent and replace it with another effective agent to minimize the amount of time a patient is on suboptimal therapy. For example, if therapy needs to be stopped due to a severe or life-threatening side effect, all antiretroviral drugs should be stopped. Once the offending drug or alternative cause for the adverse event has been determined, a plan can be made for a new antiretroviral drug regimen that does not contain the offending drug or for resuming the original regimen (if the event is attributable to another cause). All drugs in the antiretroviral regimen should then be started simultaneously, rather than starting one at a time and observing for adverse effects. Many experts recommend stopping efavirenz or nevirapine several days before stopping other drugs if possible, because these drugs have a significantly longer half-life than NRTI antiretroviral drugs (see **Long-Term Structured Treatment Interruptions**). However, if a patient has a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

When therapy is changed because of toxicity or intolerance in the context of virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible. Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, change of a single drug in a multi-drug regimen is a permissible option.

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

Management strategies for drug intolerance include:

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

Antiretroviral Treatment Failure in Infants, Children, and Adolescents

OVERVIEW (Updated February 23, 2009)

Working Group 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.**
- **When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and preserve future antiretroviral options.**
- **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.**
- **Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist.**

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

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

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

Definition of Treatment Failure (see Table 12):

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

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

- **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection using the most sensitive assay after 12 months of therapy. Children with higher HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.
- **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1000 copies/mL) more likely represents viral rebound.

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

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

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

- **Progressive neurodevelopmental deterioration:** The presence of two or more of the following findings documented on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.
- **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

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

Discordance between Viral, Immune, and Clinical Responses

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

Adequate Clinical and Immunologic Responses Despite Incomplete Virologic Response: Some patients who are maintained on combination antiretroviral therapy may maintain immunologic and clinical benefit despite detectable viral replication for up to 3 years *[5-14]*. This observation is the rationale for continuing non-suppressive antiretroviral therapy for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practicable. The risks and benefits as well as the indications for this approach are discussed in sections **Approach to the Management of Antiretroviral Treatment Failure** and **Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance**. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are the maintenance of a lower viral load or the selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either “slow-progressors” or “long-term non-progressors” without therapy.

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

Additionally, in patients with baseline severe immunosuppression, it is common to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early-treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values, prior to initiating HAART, are at higher risk of an impaired CD4 lymphocyte response to antiretroviral therapy, and may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression *[2,6,15-19]*.

Certain antiretroviral regimens may be associated with a blunted CD4 response. Treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not adjusted downward *[20]*. In adults, antiretroviral regimens containing zidovudine may also impair rise in CD4 count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine; fortunately, this suboptimal CD4 count response to therapy does not seem to confer an increased risk of clinical events *[21]*.

There are several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren’s syndrome, sarcoidosis) that are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in adults without HIV infection *[22]*.

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression:

Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response

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

Poor Immunologic and Clinical Responses Despite Virologic Suppression

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

Poor Clinical Response Despite Adequate Virologic and Immunologic Responses: Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunological and virological responses to antiretroviral therapy. Not all cases represent antiretroviral treatment failure. One of the most important reasons for new or recurrent opportunistic conditions despite achieving virologic suppression and immunologic restoration/preservation within the first months of antiretroviral treatment is immune reconstitution inflammatory syndrome (IRIS), which does not represent antiretroviral treatment failure and does not generally require discontinuation of antiretroviral treatment. Children who have suffered irreversible damage to their lungs, brain, or other organs, especially during prolonged and profound pretreatment immunosuppression, may continue to have recurrent infections or symptoms in those damaged organs, since the damage may not be reversed by immunologic improvement *[23]*. Such cases do not represent antiretroviral treatment failure and would not be expected to benefit from a change in antiretroviral regimen. Evaluation for and treatment of other causes or of conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition and malignancy, should also be undertaken before drawing a conclusion of antiretroviral treatment failure. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., PCP or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, preexisting organ damage, or other reason; such cases may be antiretroviral treatment failure and suggest that improvement in CD4 values may not necessarily represent return of complete immunologic function.

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

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

Table 12: Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children (Updated February 23, 2009)

Virologic Considerations*	• **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection of detection using the most sensitive assay after 12 months of therapy.† • **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1000 copies/mL) more likely represents viral rebound. §
Immunologic Considerations*	• **Incomplete immunologic response to therapy:** Failure by a child <5 years old with severe immune suppression (CD4 percentage <15%) to improve CD4 values by ≥5 percentage points, or as a failure by a child age 5 years old or older with severe immune suppression (CD4 <200 cells/mm^3) to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy. • **Immunologic decline:** Sustained decline of 5 percentage points in CD4 percentage below pre-therapy baseline at any age, or decline to below pre-therapy baseline in absolute CD4 cell count in children who are age 5 years and older. **
Clinical Considerations	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction. • **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

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

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

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

** Declines that represent a change to a more advanced category of immunosuppression compared to 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.

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ASSESSMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE
(Updated February 23, 2009)

Working Group Recommendations:

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

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

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

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

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

Evaluation of whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects is important for determining what changes would be best suited to the individual requirements of the child and family. Intensive family education, training in the administration of prescribed medications, and discussion of the importance of adherence to the drug regimen should be reinforced. If competing family needs are identified as impediments to adherence, social issues may need to be addressed before adherence can be improved including achieving financial or housing security, assessing concomitant mental health problems, accessing substance abuse treatment, and initiating a discussion around HIV disclosure. In some situations, clinicians may need to involve outside agencies such as child protective services to ensure support of the child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting the child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and family to improve adherence to the current or new regimen. Directly observed therapy (DOT) may be used to identify additional factors impeding adherence as well as to confirm drug administration.

Pharmacokinetic Issues

In addition to poor adherence, inadequate drug exposure can result in treatment failure *[8]*. Children consistently require higher weight-based dosing of antiretroviral drugs compared to adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range *[9]*. Causes of subtherapeutic drug levels may include failure to increase dosing for rapid growth of the child or impaired absorption because of gastrointestinal symptoms, such as vomiting or diarrhea. Drug exposure may be enhanced or reduced by administering medications with food; the clinician should review the food/fasting requirements of the regimen with the patient and caregiver. Drug interactions can alter drug metabolism; all concomitant medications, including over-the-counter medications and nutritional and herbal supplements, should be reviewed to evaluate whether they may be contributing to poor treatment response. (See **Tables 15a-e and 16a-b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***). Several recent studies suggest that genetic polymorphisms may influence pharmacokinetics and therapeutic response for a number of antiretroviral medications *[10,11]*. In some circumstances, therapeutic drug monitoring can be considered for children receiving selected drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

Suspected Drug Resistance Issues (see **Antiretroviral Drug Resistance Testing**)

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

Table 13: Assessment of Antiretroviral Treatment Failure
(Updated February 23, 2009)

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

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APPROACH TO THE MANAGEMENT OF ANTIRETROVIRAL TREATMENT FAILURE
(Updated February 23, 2009)

Working Group Recommendations:

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

General

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

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

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

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

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

antiretroviral regimen to start at a time when the child is most likely to adhere to this regimen for a sustained period.

Categories of Children with Treatment Failure and Approaches to Consider

No Viral Resistance Identified

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

Viral Resistance to Current Therapy

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

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

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

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

In the case of children for whom undetectable plasma virus is not achievable because two or more fully active agents cannot be identified, the goal is to preserve immunologic function and prevent clinical disease progression while preserving future options for new agents that are not yet available. Adult cohort studies suggest that there may be ongoing immunologic and clinical benefit if the HIV viral load can be maintained below 10,000–20,000 copies/mL *[7,8]*. Several cohort studies show a clinical benefit of remaining on antiretroviral therapy whether or not this leads to a decrease in the viral load. The principal risk associated with continuing a failing regimen is the

development of additional resistance mutations which can limit future treatment options. Interrupting therapy completely, on the other hand, may cause a rapid increase in viral load, a decrease in CD4 cell count which is frequently persistent, and an increased risk of clinical disease progression *[4]*. This approach should only be considered in special circumstances when there is a low risk that therapy interruption will quickly lead to severe immunosuppression (i.e., CD4 values at the time of therapy interruption are high). The goal of continued treatment with an incompletely suppressive regimen is to select for resistant virus with reduced viral fitness that will cause slower disease progression while reducing the risk of drug toxicity and the development of new resistance mutations to multiple classes of drugs. The overall goal of these alternative strategies is to prevent clinical and immunological progression until additional active drugs are available which can be used to design a regimen that is expected to achieve undetectable plasma viral load *[1,9-17]*. This approach should be regarded as acceptable but not ideal and these patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

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

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CHOICE OF NEXT ANTIRETROVIRAL REGIMEN FOR TREATMENT FAILURE WITH EVIDENCE OF DRUG RESISTANCE (Updated February 23, 2009)

Working Group Recommendations:

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

General

After carefully reaching a decision that a change in therapy is needed, the clinician should attempt to identify at least two but preferably three fully active antiretroviral agents on the basis of resistance testing, prior ARV exposure, acceptability to the patient, and likely adherence. This often requires the use of one or more new drug classes. Substitution or addition of a single drug to a failing regimen should be avoided as this approach is unlikely to achieve and sustain an undetectable plasma viral load, and frequently will result in additional drug resistance. A drug may be "new" to the patient but have diminished antiviral potency due to the presence of drug mutations that confer cross-resistance within a drug class. In children who are changing therapy due to occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher levels within the central nervous system *[1-4]*.

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

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

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

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

Choice of the new dual NRTI component is particularly important when constructing a regimen as the choice of an insufficiently potent NRTI may result in the selection of additional NRTI-related drug mutations. Resistance testing is essential to properly select a potent NRTI combination and interpretation of these results should take place in collaboration with an expert in pediatric HIV infection (see **Antiretroviral Drug Resistance Testing**). In this case, use of a triple class regimen or the use of a novel agent may be necessary.

If a patient has substantial pre-existing resistance, or if the initial regimen contained drugs from all 3 major classes (NRTI, NNRTI, and PI), the drug resistance profile and management approach is likely to resemble that of a patient who has had multiple antiretroviral regimen failures (see **Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered**). In this situation, a new regimen with only two fully active agents may be the best available option. Lopinavir/ritonavir-based regimens have shown durable antiretroviral activity in antiretroviral treatment-experienced children, including children with prior PI therapy *[5-7]*. Adult studies of treatment-experienced patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitor), coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced, multiresistant patients is associated with better virologic responses *[8,9]*. **Appendix B: Characteristics of Available Antiretroviral Drugs** and **Supplement I: Pediatric Antiretroviral Drug Information** provide more detailed information on drug formulation, pediatric and adult dosing, and toxicity as well as discussion of available pediatric data for the approved antiretroviral drugs, including new drugs in existing classes, such as darunavir, and new classes of drugs such as CCR5 antagonists and integrase inhibitors. Maraviroc (CCR5 inhibitor) and raltegravir (integrase inhibitor) are approved for use in adolescents 16 years or older and can be considered for management of older adolescents with multi-drug failure; pediatric trials are underway or in development.

It is sometimes possible to reintroduce previously prescribed drugs that were originally poorly tolerated or for which adherence was poor, particularly if antiretroviral resistance had not developed and the underlying reasons for prior difficulties can be overcome, such as being able to switch from liquid to pills. Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir *[10-12]*. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children might be justified and is ideally done in the framework of a clinical trial (see **The Use of Antiretroviral Agents Not Approved for Use**

in Children). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

The HIV entry inhibitor enfuvirtide (T-20) has been approved for use in heavily treatment-experienced patients based on potent antiretroviral activity in heavily treatment-experienced adults, and has been approved for use in children age 6 years and above *[13,14]*. Studies have helped establish safety, appropriate dosing and efficacy of enfuvirtide in treatment experienced children ≥6 years old; this therapy has the disadvantage of administration by subcutaneous injection twice daily *[15,16]*. Enfuvirtide adherence in adolescent populations remains a unique challenge when compared to younger children. However, this agent should be considered as an option when designing a new regimen for pediatric populations who have failed treatment with multiple classes of antiretroviral medications.

Pharmacokinetic studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that pharmacokinetic targets for both PIs can be achieved or exceeded when used in combination in adults *[17-19]* and in children *[20-22]*. Pharmacokinetic studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs *[23,24]*. Kosolaraksa treated 50 PI-naïve but NRTI+/-NNRTI experienced Thai children with a combination of lopinavir/ritonavir (230/57.5 mg/m^2 twice daily) and saquinavir (50 mg/kg twice daily, max. dose 1000 mg) and demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks for ≥50% of patients. The regimen was well tolerated but hyperlipidemia was common. The use of multi-drug regimens, sometimes including up to three PIs and/or two NNRTIs, has shown efficacy in a pediatric case series *[25]* but should be used cautiously due to its complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring (TDM) may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity due to the presence of drug resistance mutations (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

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

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

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

Even when NRTI drug resistance mutations are present, there can be immunologic and clinical benefit despite persistent viremia when patients are treated with lamivudine monotherapy or when they are treated with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir *[26,27]*.

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

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low *[28-30]*. 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" non-suppressive regimens, since such use of a single fully active agent will quickly lead to diminished activity of that agent. When clinical or immunologic deterioration occurs in such cases, it is often appropriate to use investigational agents or agents approved for older age groups as a second fully active drug in the new regimen (see **The Use of Antiretroviral Agents Not Approved for Use in Children**).

Table 14. 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 * (Updated February 23, 2009)

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

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

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THE USE OF ANTIRETROVIRAL AGENTS NOT APPROVED FOR USE IN CHILDREN

(Updated February 23, 2009)

Working Group Recommendations:

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

It has long been practice for physicians, especially pediatricians, to prescribe medications in "off-label" situations, meaning for indications or populations that do not fall within the FDA's official indication. The relatively small market for pediatric antiretroviral drugs and few children available for clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some antiretroviral drugs at the same time they are approved in adults. Pediatric HIV specialists may need to prescribe these agents because of high levels of resistance seen in heavily-treated children and adolescents, and improvements in tolerability and ease of adherence with newer agents with less frequent dosing.

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

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

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

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

Even more difficult than the potential for adverse effects has been the difficulty of dosing of antiretrovirals in pediatric patients. As absorption, hepatic metabolism and excretion change with age, so will drug levels change in children *[1]*. The difficulty in dosing children as they increase in weight is exacerbated by changing pharmacokinetics. The direct extrapolation of the adult dose to a pediatric dose, based either on body weight or body surface area, has been shown in clinical trials of several antiretroviral agents to underestimate the appropriate pediatric dose.

In summary, the use of antiretroviral agents without a pediatric indication is an absolute necessity for the treatment of some children with HIV, but 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 availability of suitable clinical trials.**

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ROLE OF THERAPEUTIC DRUG MONITORING IN MANAGEMENT OF TREATMENT FAILURE (Updated February 23, 2009)

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

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

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

There are two main situations where 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 subject whose virus has a reduced susceptibility to that drug.

For TDM to be useful there needs to be a clearly defined relationship between antiretroviral concentrations and anti-HIV effects *[3-5]*. This association is strongest with PI and NNRTI drugs *[6]*, but maintaining adequate NRTI serum concentrations has also been shown to be important for maximal anti-HIV activity *[7]*. The exposure-toxicity response relationship is less well defined for NRTI drugs, but has been determined for some agents *[4]*. Concentration-response relationships have been established with minimum plasma concentrations (C_{min} or C_{trough}) or area under the curve (AUC), but the optimal measure is not defined for all antiretroviral drugs *[8]*.

In patients with wild-type virus, **Table 15** presents recommendations for the minimum target trough concentrations of PIs and NNRTIs. In antiretroviral-experienced patients, choosing minimum target trough concentration should be based on results of resistance testing *[9-11]*. Although it is intrinsically difficult to demonstrate benefit of TDM using double-blind studies, limited data suggest targeted concentrations can be achieved with TDM and clinical responses improved with increased or modified doses, and that TDM information can be helpful in decision making *[6,12-16]*. The clinician should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

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

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

Current limitations for pediatric antiretroviral TDM include:

- Prolonged time for laboratory processing, in the face of potentially diminishing benefit the longer the patient is on inadequate therapy;

- Difficulties in coordinating sample collections at appropriate times make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results *[17,18]*;
- Single trough measurements within the target range do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third party reimbursement of costs associated with TDM.

Table 15. Suggested Minimum Target Trough Concentrations (From *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* - Table 10)
(Updated November 3, 2008)

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

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DISCONTINUATION OR INTERRUPTION OF THERAPY (Updated October 26, 2006)

General

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

Short-Term Therapy Interruption

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

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

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation *[1-4]*. As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in a slower rate of drug clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and Hispanics *[3,4]*. To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs (i.e., NRTI backbone or PI) for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known. Detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation *[4]*. An alternative is to substitute a PI for up to 4 weeks prior to the interruption of all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective strategy. There is no information, in children and because the pharmacokinetics of these agents are different in children, the recommendations for adults may not be applicable *[5-7]*.

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

Long-Term Structured Treatment Interruptions

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

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

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

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

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

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Antiretroviral Drug Resistance Testing

(Updated February 23, 2009)

Working Group Recommendations

- **Antiretroviral drug resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.**
- **Antiretroviral drug resistance testing is recommended prior to changing therapy for treatment failure.**
- **Resistance testing in the setting of virological failure should be obtained when patients have a viral load >1,000 copies/mL while still on the failing regimen, or within 4 weeks of discontinuation of the regimen.**
- **The absence of detectable resistance to a drug does not insure that its use will be successful, especially if it 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, the history of past use of antiretroviral agents is important in making decisions regarding the choice of new agents for patients with virologic failure.**
- **Viral Coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist.**
- **Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral regimen in a pediatric patient.**

OVERVIEW OF HIV DRUG RESISTANCE AND RESISTANCE ASSAYS

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

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

Genotypic Assays

Genotypic assays for PR and RT inhibitors are based on PCR amplification and analysis of the RT and PR coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance associated mutations in plasma samples containing approximately 1000 copies/mL or more of HIV RNA, and results are generally available within 1–2 weeks of sample collection *[2]*. Interpretation of test results requires knowledge of

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

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

Phenotypic Assays

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

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

Tropism (Viral Coreceptor Use) Assays

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

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

Use of Resistance Assays in Determining Initial Treatment

Mother-to-child transmission and horizontal transmission of drug-resistant HIV strains have been well documented and are associated with suboptimal virologic response to initial antiretroviral therapy *[13-17]*. Drug resistant variants of HIV may persist for months after birth in infected infants *[18]* and impair the response to antiretroviral therapy *[19]*. Consequently, antiretroviral drug resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.

Use of Resistance Assays in the Event of Virologic Failure

Several studies *[2,4-10]* have been performed in adults indicating that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Although not yet confirmed in children *[20]*, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure. Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction as virologic failure in the setting of combination antiretroviral therapy may be associated with resistance to only one component of the regimen *[1]*. Poor adherence should be suspected when no evidence of resistance is identified to a failing regimen.

Limitations of Current Resistance and Tropism Assays

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

Although drug resistance may be detected in infants, children, and adults who are not receiving therapy at the time of the assay loss of detectable resistance and reversion to predominantly wild-type virus often occurs in the first 4–6 weeks after antiretroviral drugs are stopped *[21-23]*. As a result, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued. The absence of detectable resistance to a drug at the time of testing does not insure that its future use will be successful *[24]*, especially if it 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 an individual with prior treatment failure(s). (See **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**)

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Managing Complications of HIV Infection

(Updated October 26, 2006)

The Pediatric Antiretroviral Treatment Guidelines includes the supplements **Managing Complications of HIV Infection** and **Adverse Drug Effects**. These supplements contain guidelines on two important issues in pediatric HIV infection—nutrition and pain management—as well as separate sections on specific adverse drug effects, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The U.S. Public Health Service, HIV Medicine Association of the Infectious Disease Society of America, and Pediatric Infectious Disease Society jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and infected children, as well as in adults, which are available at **http://aidsinfo.nih.gov/guidelines** .

Conclusion

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral drugs and newer classes of drugs are approved. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional antiretroviral drugs become approved and optimal use of these drugs in children becomes better understood, the Working Group 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 seek consultation with an expert in such care.

APPENDIX A
Tables and Figures

Appendix Table 1: 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

(Updated February 28, 2008)

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

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

Appendix Table 2: 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)*
(Updated February 28, 2008)

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

* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008 in press.

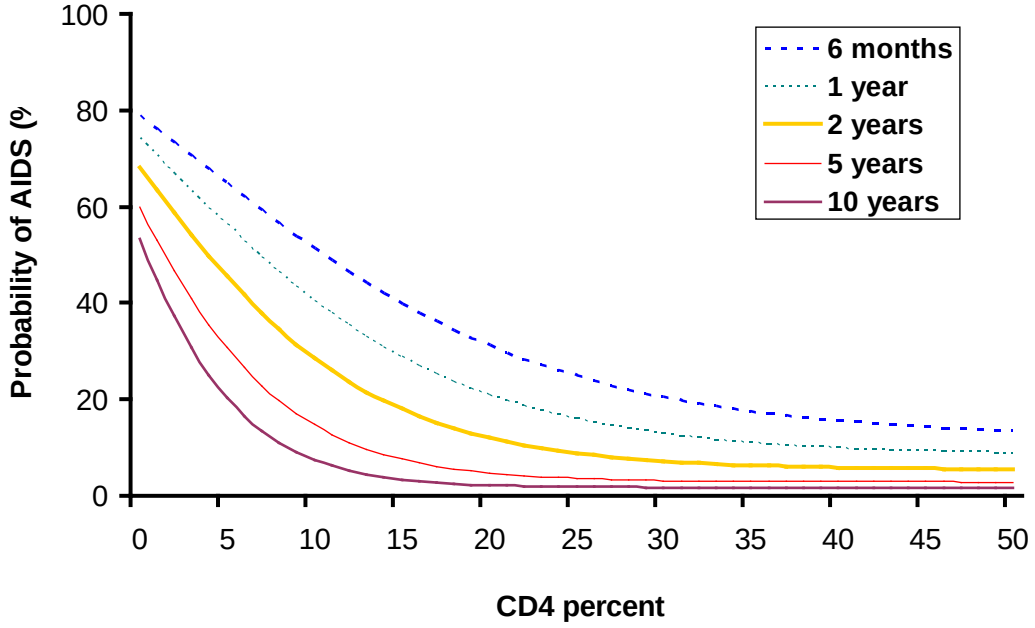
Appendix Table 3: Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4+ T Cell Percentage with Long-Term Risk for Death in HIV-Infected Children* (Updated April 17, 1998)

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

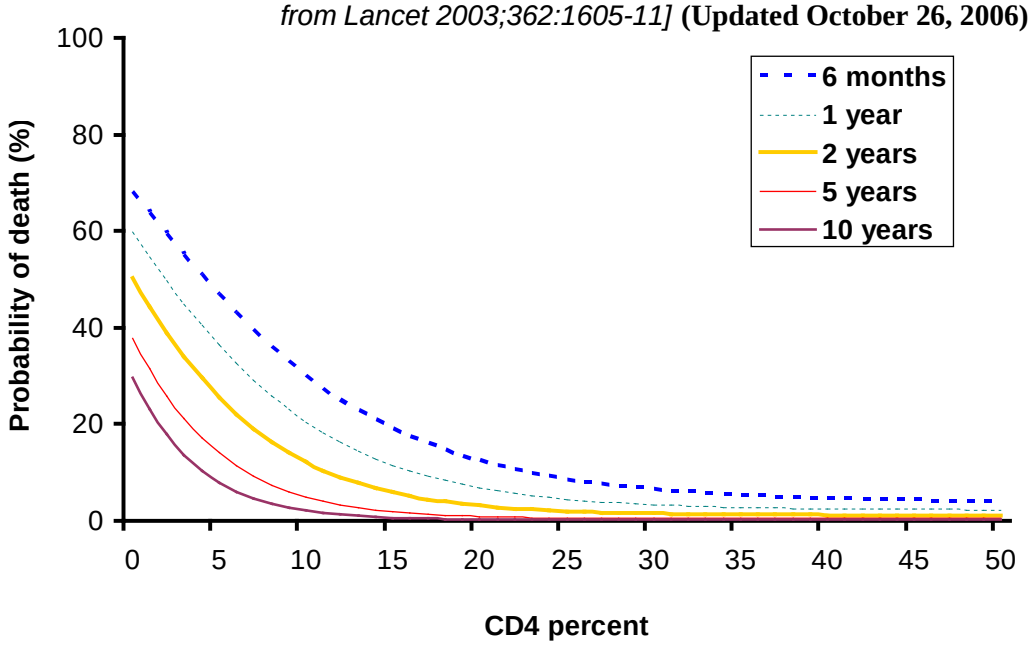
* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.
† Mean follow-up: 5.1 years.
§ Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.
¶ Mean age: 3.4 years.

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

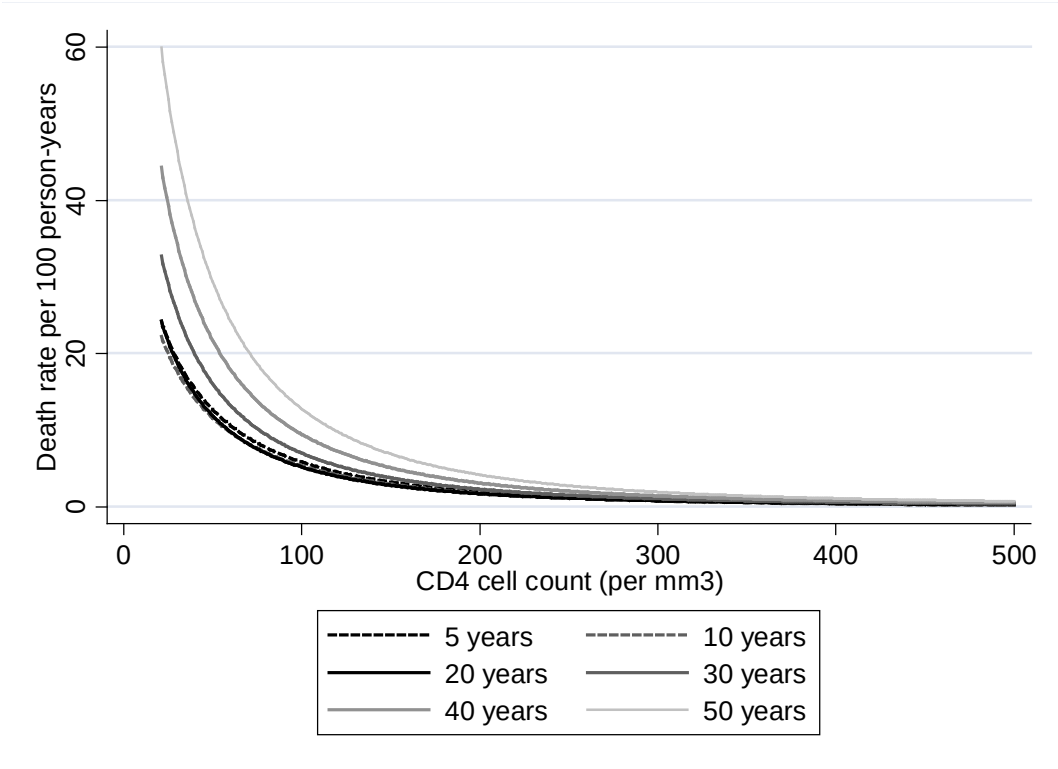
Appendix Figure 1: Estimated probability of AIDS within 12 months by age and CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**



Appendix Figure 2: Estimated probability of death within 12 months by age and CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**

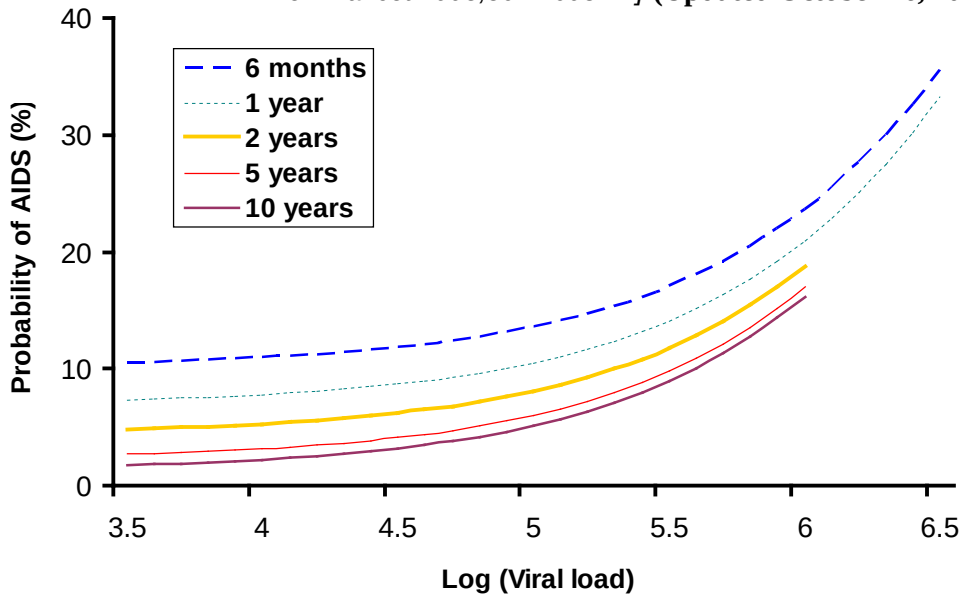


Appendix Figure 3: Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study* **(Updated February 28, 2008)**

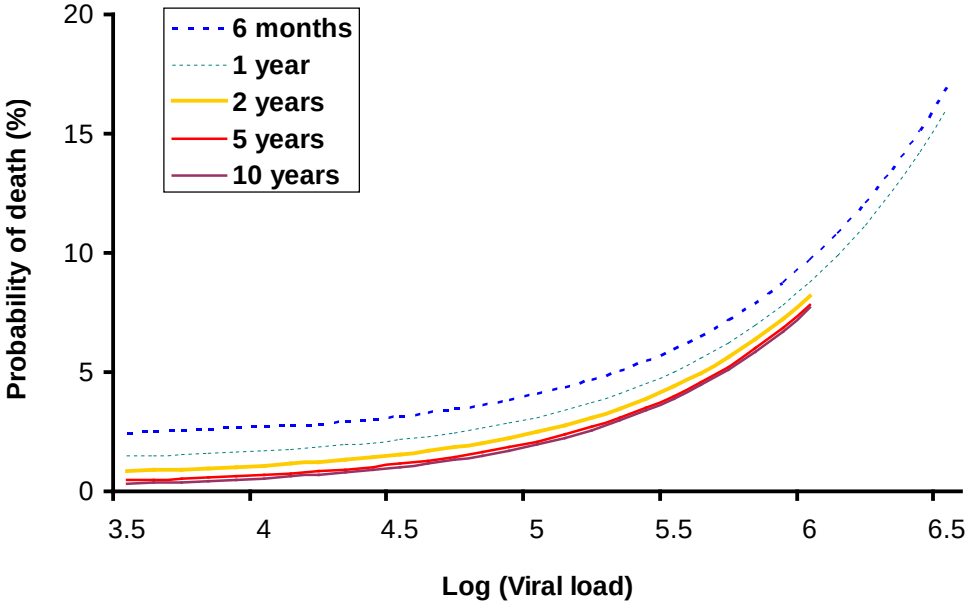


* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. J Infect Dis 2008 in press.

Appendix Figure 4: Estimated probability of AIDS within 12 months by age and HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**



Appendix Figure 5: Estimated probability of death within 12 months by age and HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**



APPENDIX B
Characteristics of Available Antiretroviral Drugs

Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs/NtRTIs) * †

Abacavir *(ABC, ZIAGEN)*
See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Patients should be tested for the HLA-B*5701 allele prior to initiating therapy to predict risk of ABC hypersensitivity. Patients who are positive for HLA-B*5701 should not be given ABC and increased potential for ABC hypersensitivity should be noted in their medical records.

Preparations: Pediatric oral solution: 20 mg/mL. Tablets: 300 mg, 300 mg (scored).

Tablets in combination with zidovudine (ZDV) and lamivudine (3TC): TRIZIVIR – 300 mg ZDV, 150 mg 3TC, and 300 mg ABC.

Tablets in combination with 3TC: EPZICOM – 300 mg 3TC and 600 mg ABC.

Dosing
Neonatal/Infant dose: Not approved for use in infants aged <3 months.

Pediatric (age ≥3 months) dose: 8 mg per kg of body weight (maximum dose 300 mg) twice daily.

(New dosing recommendations using the scored tablets will be available for pediatric patients when the new product becomes available.)

Adolescent dose: Data from clinical trials support the use of the adult dose of 300 mg twice daily for adolescents.

Adult dose (>16 years): 300 mg twice daily or 600 mg once daily.

Adult dose of TRIZIVIR: One tablet twice daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or patients with impaired hepatic function.

Adult dose of EPZICOM: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute.

Dosing of ABC in patients with hepatic impairment: Insufficient data are available to recommend a dosage in patients with hepatic impairment.

Major Toxicities
More common: Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.

Less common (more severe): Serious and sometimes fatal hypersensitivity reactions have been associated with ABC: approximately 5% of adults and children (rate varies by race/ethnicity) receiving ABC develop a potentially fatal hypersensitivity reaction. Hypersensitivity to ABC is a multi-organ clinical syndrome usually characterized by a sign or symptom in >2 of the following groups: 1) fever; 2) rash; 3) gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain; 4) constitutional, including malaise, fatigue, or achiness; and 5) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. Patients suspected of having a hypersensitivity reaction should have ABC stopped and NOT RESTARTED BECAUSE HYPOTENSION AND DEATH HAVE OCCURRED UPON RECHALLENGE. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.

Rare: Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction.

Drug Interactions
See: **Table 15c** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- ABC does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should

not cause changes in clearance of agents metabolized through these pathways, such as PIs and NNRTIs.

- ABC is metabolized by alcohol dehydrogenase and glucuronyltransferase. Alcohol increases ABC levels by 41%.

Special Instructions

- Can be given without regard to food.
- Patients and parents must be cautioned about the risk of serious hypersensitivity reaction. A medication guide and warning card should be provided. Patients experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).
- Because of concerns for possibly severe hypersensitivity reactions, patients should not interrupt and restart therapy without consulting their physicians.
- Patients should be tested for the HLA-B*5701 allele prior to initiating therapy to predict risk of ABC hypersensitivity. Patients who are positive for HLA-B*5701 should not be given ABC and increased potential for ABC hypersensitivity should be noted in their medical records.

Didanosine *(dideoxyinosine, ddI, VIDEX)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL.

VIDEX EC delayed-release capsules (enteric-coated beadlets): 125 mg, 200 mg, 250 mg, and 400 mg. Generic ddI delayed-release capsules: 200 mg, 250 mg, and 400 mg.

Dosing

Neonatal/Infant dose (infants aged 2 weeks to 8 months) usual dose of oral solution: 100 mg per m^2 of body surface area every 12 hours.

Pediatric (age >8 months) usual dose of oral solution: In combination with other antiretrovirals: 120 mg per m^2 of body surface area every 12 hours; clinical studies have used a pediatric dose range of 90–150 mg per m^2 of body surface area every 12 hours. In treatment-naïve children aged 3–21 years, 240 mg per m^2 of body surface area once daily (maximum 400 mg) has been used with good viral suppression (PACTG 1021).

Dosing Recommendations for ddI Delayed Release Capsules in Pediatric Patients (ages 6–18 years and weighing ≥20 kg and able to swallow capsules)

Body Weight	Dose
20 kg to less than 25 kg	200 mg once daily
25 kg to less than 60 kg	250 mg once daily
At least 60 kg	400 mg once daily

Adolescent/Adult dose:

- ddI oral solution: Body weight ≥60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily. The total daily dose (400 mg or 250 mg, depending on weight) may be administered once daily in adolescents/adults to improve compliance; however, the preferred dosing frequency is twice daily because there is more evidence to support the effectiveness of this regimen.
- ddI delayed release capsule formulation: Body weight ≥60 kg: 400 mg once daily. Body weight <60 kg: 250 mg once daily.

ddI in combination with tenofovir (TDF) (adults): For adult patients with body weight ≥60 kg and CrCl ≥60 mL/min receiving combination therapy with TDF, the recommended dose of ddI delayed release capsule formulation is 250 mg once daily. For adult patients with body weight <60 kg and CrCl ≥60 mL/min, limited data suggest that a ddI delayed release capsule formulation dose of 200 mg once daily may be used. There are no data concerning this combination in children or adolescents <18 years of age or in patients with CrCl <60 mL/min.

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

Major Toxicities

More common: Diarrhea, abdominal pain, nausea, and vomiting.

Less common (more severe): Peripheral neuropathy (dose related, more common in patients with advanced disease), electrolyte abnormalities, and

hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Risk factors for lactic acidosis include gender (women at higher risk), obesity, and prolonged nucleoside exposure. Pancreatitis (fatal and nonfatal, dose related, less common in children than adults, more common in adults when used in combination with TDF), increased liver enzymes, and retinal depigmentation, retinal changes, and optic neuritis have been reported. The combination of stavudine (d4T) with ddI may result in enhanced toxicity (increased risk of fatal and non-fatal cases of lactic acidosis, hepatotoxicity, or pancreatitis). Fatal lactic acidosis has been reported in pregnant women receiving d4T and ddI. This combination should not be used unless the potential benefit clearly outweighs potential risk. Hepatic toxicity and hepatic failure (patients with preexisting liver dysfunction have an increased frequency of liver function abnormalities). Fat redistribution.

Drug Interactions

See: **Table 15c** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Absorption:* The presence of antacids in the ddI suspension and tablets has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by the appropriate timing of doses.
- *Mechanism unknown:* ddI serum concentrations are increased when coadministered with TDF. A dose reduction is recommended when ddI is coadministered with TDF and patients should be monitored closely for ddI-associated adverse effects.
- Allopurinol and ganciclovir increase ddI concentrations while methadone decreases ddI concentrations. It is recommended that allopurinol not be administered to patients receiving ddI.
- *Renal elimination:* Drugs that decrease renal function could decrease clearance.
- *Enhanced toxicity:* ddI mitochondrial toxicity is enhanced by ribavirin and it is recommended that these drugs not be coadministered.
- *Overlapping toxicities:* Increased risk of pancreatitis and peripheral neuropathy with some NRTIs (e.g., d4T). Combination of d4T and ddI 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.

Special Instructions

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

Emtricitabine *(FTC, EMTRIVA)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 200 mg. Oral solution: 10 mg/mL.

Tablets in combination with tenofovir (TDF): TRUVADA – 200 mg FTC and 300 mg TDF.

Tablets in combination with TDF and efavirenz (EFV): ATRIPLA – 200 mg FTC and 300 mg TDF and 600 mg EFV.

Dosing

Neonatal/Infant dose: Not approved for use in neonates/infants <3 months of age.

Pediatric (age 3 months through 17 years) dose: Oral solution: 6 mg per kg of body weight (maximum dose 240 mg) once daily. Capsules (for patients weighing >33 kg): 200 mg once daily.
Adolescent (age ≥18 years)/Adult dose: Capsules: 200 mg once daily. Oral solution: 240 mg (24 mL) administered once daily.

Adult dose of TRUVADA: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <30 mL/minute or patients requiring hemodialysis.

Adult dose of ATRIPLA: One tablet once daily. Because this is a fixed dose combination product, it

should not be used in patients with creatinine clearance of <50 mL/minute.

Dosing of FTC in patients with renal insufficiency: The effects of renal impairment on FTC pharmacokinetics in pediatric patients are not known. 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.

Major Toxicities
More common: Headache, insomnia, diarrhea, nausea, rash, and skin discoloration (hyperpigmentation on palms and/or soles, predominantly observed in non-Caucasian patients).

Less common (more severe): Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. In patients coinfected with HIV and HBV, exacerbations of hepatitis have occurred when changes have been made from FTC-containing regimens to non-FTC-containing regimens.

Drug Interactions
See: **Table 15c** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism:* No inhibition of CYP450 isoenzymes or hepatic glucuronidation enzymes.
- *Renal elimination:* Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion).
- *Other NRTIs:* Do not use in combination with lamivudine because of the similar resistance profiles and no potential additive benefit.

Special Instructions

- Can be given without regard to food. It is recommended that ATRIPLA be administered on an empty stomach because it contains EFV.
- Patients should be screened for HBV infection before starting therapy; exacerbation of hepatitis has been reported in patients after discontinuation of FTC. HIV/HBV-coinfected patients should have close clinical and laboratory monitoring for at least several months after stopping therapy with FTC.
- Oral solution should be refrigerated. Can be kept at room temperatures up to 77°F (25°C) if used within 3 months.

Lamivudine *(3TC, EPIVIR, EPIVIR HBV)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Solution: 10 mg/mL (*EPIVIR*); 5 mg/mL (*EPIVIR HBV*[λ]). Tablets: 150 mg (scored) and 300 mg (*EPIVIR*); 100 mg (*EPIVIR HBV*[λ]).

Tablets in combination with zidovudine (ZDV): COMBIVIR – 300 mg ZDV and 150 mg 3TC.

Tablets in combination with ZDV and abacavir (ABC): TRIZIVIR – 300 mg ZDV, 150 mg 3TC, and 300 mg ABC.

Tablets in combination with ABC: EPZICOM – 300 mg 3TC and 600 mg ABC.

Dosing
Neonatal/Infant dose (infants aged <30 days): 2 mg per kg of body weight twice daily.

Pediatric dose: 4 mg per kg of body weight (maximum dose, 150 mg) twice daily.

Dosing Recommendations for Epivir 150 mg Scored Tablets (≥14 kg)

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

Adolescent (age ≥16 years)/Adult dose: Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily. Body weight <50 kg: 4 mg per kg of body weight (maximum dose, 150 mg) twice daily.
Adolescent (age >12 years)/Adult dose of COMBIVIR: One tablet twice daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50

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

mL/minute or patients with impaired hepatic function.

Adolescent (weight ≥40 kg)/Adult dose of TRIZIVIR: One tablet twice daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or patients with impaired hepatic function.

Adult dose of EPIZCOM: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute.

Dosing of 3TC 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.

Major Toxicities
More common: Headache, fatigue, and nausea, which generally decrease over time; decreased appetite, diarrhea, skin rash, and abdominal pain.
Less common (more severe): Pancreatitis (primarily seen in children with advanced HIV infection receiving other additional medications), peripheral neuropathy, anemia, decreased neutrophil count, increased liver enzymes, and fat redistribution. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. In patients coinfected with HIV and HBV, exacerbations of hepatitis have occurred when changes have been made from 3TC-containing regimens to non-3TC-containing regimens.

Drug Interactions
See: **Table 15c** from 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.
- *Other NRTIs:* Do not use in combination with FTC because of the similar resistance profiles and lack of potential additive benefits.

Special Instructions

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

Stavudine *(d4T, ZERIT)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 15 mg, 20 mg, 30 mg, and 40 mg. Solution: 1 mg/mL.

Generic: Stavudine capsules and solution have been approved by the FDA for manufacture and distribution in the United States.

Dosing
Neonatal/Infant dose (age birth to 13 days): 0.5 mg per kg of body weight every 12 hours.

Pediatric dose (age 14 days up to weight of 30 kg): 1 mg per kg of body weight every 12 hours.

Adolescent (weight ≥30 kg)/Adult dose: Body weight 30–<60 kg: 30 mg twice daily. Body weight ≥60 kg: 40 mg twice daily
Dosing of d4T 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.

Major Toxicities
More common: Headache, gastrointestinal disturbances, skin rashes, and lipoatrophy.

Less common (more severe): Peripheral neuropathy, pancreatitis, and lipodystrophy/lipoatrophy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. The combination of d4T with didanosine (ddI) may result in enhanced toxicity (increased risk of fatal and non-fatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefits clearly outweigh the potential risks.

Rare: Increased liver enzymes; rapidly progressive ascending neuromuscular weakness.
Drug Interactions
See: **Table 15c** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Renal elimination:* Drugs that decrease renal function could decrease d4T clearance.
- *Other NRTIs*: Should not be administered in combination with zidovudine (poor antiretroviral effect).
- *Overlapping toxicities*: Combination of d4T and ddI 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.

Special Instructions

- Can be given without regard to food.
- For oral solution: shake well and keep refrigerated. Stable for 30 days.
- Decrease dose in renal dysfunction.
- Higher incidence of lactic acidosis and hepatic steatosis than with other NRTIs.

Tenofovir *(TDF, VIREAD)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablet: 300 mg.

Tablets in combination with emtricitabine (FTC): TRUVADA – 200 mg FTC and 300 mg TDF

Tablets in combination with FTC and efavirenz (EFV): ATRIPLA – 200 mg FTC, 300 mg TDF, and 600 mg EFV.

Dosing

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

Pediatric dose: Not approved for use in children aged <18 years; only commercially available preparation is 300 mg tablets. Clinical trials are under way in children with investigational formulations (investigational dose: children aged 2–8 years, 8 mg per kg of body weight once daily; children aged >8 years, median dose of 210 mg per m^2 of body surface area once daily, maximum dose of 300 mg once daily).

Adolescent (age ≥18 years)/Adult dose: 300 mg once daily.

Adult dose of TRUVADA: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <30 mL/minute or patients requiring hemodialysis.

Adult dose of ATRIPLA: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute.

TDF in combination with didanosine (ddI) (adults): For adult patients with body weight ≥60 kg receiving combination therapy with TDF, the recommended dose of ddI delayed release capsule formulation is 250 mg once daily. For adult patients with body weight <60 kg, limited data suggest that a ddI delayed release capsule formulation dose of 200 mg once daily may be used. There are no data concerning this combination in children or adolescents <18 years of age.

TDF in combination with atazanavir (ATV) (adults): 300 mg ATV + 100 mg ritonavir (RTV) + 300 mg TDF, all once daily. Only ATV boosted with RTV should be used in combination with TDF.

Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

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. TDF caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been shown in both adults and children taking TDF for 48 weeks; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate has been observed in animal studies at high exposure levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored.

Drug Interactions
See: **Table 15c** from 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 TDF.
- *Other NRTIs:* ddI serum concentrations are increased when coadministered with TDF.
- *PIs:* TDF decreases ATV plasma concentrations. In adults, it is recommended that when ATV is coadministered with TDF, ATV 300 mg should be given with RTV 100 mg and TDF 300 mg, all as a single daily dose with food. ATV without RTV should not be coadministered with TDF. In addition, ATV and lopinavir/ritonavir (LPV/RTV) increase TDF concentrations and could potentiate TDF-associated renal toxicity**.**

Special Instructions

- TDF can be administered without regard to food, although absorption is enhanced when administered with a high fat meal. It is recommended that ATRIPLA be administered on an empty stomach because it contains EFV.
- When coadministered, ddI delayed release capsule formulation and TDF may be taken under fasted conditions or with a light meal.
- Patients should be screened for HBV prior to use of TDF. Severe acute exacerbation of hepatitis can occur when TDF is discontinued, so hepatic function should be monitored for several months after therapy with tenofovir is stopped.

Zidovudine *(ZDV, AZT, RETROVIR)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

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

Tablets in combination with lamivudine (3TC): COMBIVIR – 300 mg ZDV and 150 mg 3TC.
Tablets in combination with 3TC and abacavir (ABC): TRIZIVIR – 300 mg ZDV, 150 mg 3TC, and 300 mg ABC.

Dosing
Dose for premature infants for prevention of transmission or treatment (standard neonatal dose may be excessive in premature infants): 1.5 mg per kg of body weight (intravenous) or 2 mg per 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 (neonates <30 weeks gestational age).

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

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

Recently approved mg per kg dosing can also be used per table.

Dosing Recommendations for Zidovudine in Pediatric Patients (age 6 weeks to <18 years)

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

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

Intravenous dosing: Intermittent infusion: 120 mg per m^2 of body surface area every 6 hours. Continuous infusion: 20 mg per m^2 of body surface area per hour.

Adolescent (age ≥18 years)/Adult dose: 200 mg 3 times a day or 300 mg twice daily.

Adolescent/Adult dose of COMBIVIR: One tablet twice daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or patients with impaired hepatic function.

Adolescent/Adult dose of TRIZIVIR: One tablet twice daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or patients with impaired hepatic function.

Dosing of ZDV 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 patients on hemodialysis or peritoneal dialysis.

Dosing of ZDV in patients with hepatic impairment: Limited data suggest decreased dosing may be required in patients with hepatic impairment.

Major Toxicities
More common: Hematologic toxicity, including granulocytopenia and anemia. Headache, malaise, nausea, vomiting, and anorexia.

Less common (more severe): Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat redistribution.

Rare: Increased risk of hypospadias after first trimester exposure to ZDV observed in one cohort study.

Drug Interactions
See: **Table 15c** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

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

Special Instructions

- Can be given without regard to food.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary in some patients.
- Infuse intravenous loading dose or intermittent infusion dose over 1 hour.
- For intravenous solution: Dilute with 5% dextrose injection solution to concentration ≤4 mg/mL; refrigerated diluted solution is stable for 24 hours.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs) * †

Efavirenz *(EFV, SUSTIVA)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 50 mg and 200 mg. Tablets: 600 mg.

Tablets in combination with emtricitabine (FTC) and tenofovir (TDF): ATRIPLA – 200 mg FTC and 300 mg TDF and 600 mg EFV.

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

Pediatric dose (≥3 years of age and weight ≥10 kg): Administer EFV once daily:

Body Weight		
Kilograms	Pounds	EFV dose (mg)*
10–<15	22–<33	200
15–<20	33–<44	250
20–<25	44–<55	300
25–<32.5	55–<71.5	350
32.5–<40	71.5–<88	400
≥40	≥88	600

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

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

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

Adult dose of ATRIPLA: One tablet once daily. Because this is a fixed dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute and should not be used in pediatric patients <40 kg where the EFV dose would be excessive.
EFV in combination with fos-amprenavir (f-APV) (adults): 700 mg f-APV + 100 mg ritonavir (RTV) twice daily + 600 mg EFV once daily; or 1,400 mg f-APV + 300 mg RTV + 600 mg EFV, all once daily (ARV-naïve patients only).

EFV in combination with atazanavir (ATV) (adults): 300 mg ATV + 100 mg RTV + 600 mg EFV, all once daily with food. Only ATV boosted with RTV should be administered with EFV.

EFV in combination with indinavir (IDV) (adults): 1,000 mg IDV three times daily + 600 mg EFV once daily (higher doses of IDV are required).

EFV in combination with lopinavir (LPV)/RTV (adolescents >12 years/adults): 600 mg LPV/150 mg RTV (three tablets) twice daily + 600 mg EFV once daily.

EFV in combination with LPV/RTV (children ages 6 months to 12 years): see dosing tables under **Lopinavir/Ritonavir**; EFV dosing is the same but LPV/RTV dosing differs when used in combination.

EFV in combination with maraviroc (MVC) (adults): MVC 600 mg twice daily + 600 mg EFV once daily.

Dosing of EFV in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.

Major Toxicities
More common: Skin rash, increased transaminase levels. Central nervous system abnormalities (e.g., somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) primarily reported in adults.

Rare: In cynomolgus monkeys, prenatal EFV exposure has been associated with central nervous system congenital abnormalities in infant monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe central nervous system defects in five infants after first trimester exposure to EFV-containing regimens (3 meningomyelocoeles and 2 Dandy-Walker malformations), EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). EFV use in the first trimester of pregnancy should be avoided and women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to the fetus and need to avoid pregnancy before initiating EFV therapy.

Drug Interactions
See: **Tables 14, 15b, and 16b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

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

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

Etravirine *(ETR, INTELENCE, TMC125)*
See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 100 mg.

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

Pediatric dose: Not approved for use in children.

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

Dosing of ETR in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

Dosing of ETR in patients with renal impairment: No dose adjustments are required in patients with renal impairment.

Major Toxicities
More common: Nausea, rash. Rash is generally mild to moderate, occurring primarily in the second week of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. Patients with a history of NNRTI-related rash do not appear to be at increased risk of developing rash with ETR.

Less common (more severe): Severe rash including Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme occurred in >0.1% of patients during clinical trials. Discontinue treatment if severe rash develops.

Drug Interactions
See: **Tables 14, 15b, and 16b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- Metabolism: ETR is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19. There are multiple drug interactions. [§]
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- ETR **should not** be coadministered with the following antiretrovirals: tipranavir/ritonavir (RTV), fosamprenavir/RTV, atazanavir/RTV, RTV, unboosted PI's, and any of the NNRTIs. Appropriate doses of other antiretroviral drugs when used with ETR are being evaluated.

Special Instructions

- ETR should always be taken following a meal. AUC is decreased by about 50% when taken on an empty stomach.
- Tablets are sensitive to moisture and should be stored at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow the tablets may disperse the tablets in a small amount of water. Once dispersed, the patients should stir the dispersion well and consume it immediately. The glass should be rinsed with water several times and each of the rinses completely swallowed to ensure that the entire dose is consumed.

Nevirapine *(NVP, VIRAMUNE)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 200 mg. Suspension: 10 mg/mL.

Dosing
Note: NVP is initiated at a lower dose and increased in a stepwise fashion. This allows induction of cytochrome P450 metabolizing enzymes, which results in increased clearance of drug. The occurrence of rash may be diminished by the stepwise increase in dose. The following suggested incremental increases in dose are based on days on treatment (not age).

Neonatal/Infant dose (age ≤14 days): Dose used for NVP prophylaxis of mother-to-child HIV transmission was 2 mg per kg body weight given as a single dose between birth and age 3 days. Treatment dose not defined for infants <14 days of age.

Pediatric dose (15 days and older): Initiate therapy with 150 mg per m^2 of body surface area (maximum dose, 200 mg) administered once daily for the first 14 days. If no rash or untoward effects, increase to full dose, 150 mg per m^2 of body surface area administered twice daily (maximum dose, 200 mg twice daily); younger children (e.g., age ≤8 years) may require a higher dosage (i.e., 200 mg per m^2 of body surface area twice daily). The total daily dose should not exceed 400 mg.

Calculation of the Volume of VIRAMUNE Oral Suspension (10 mg/mL) Required for Pediatric Dosing Based on a Dose of 150 mg per m^2 of Body Surface Area*	
BSA range (m^2)	**Volume (mL)**
0.06 – 0.12	1.25
0.12 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
>1.25	20

*Table based on dosing at 150 mg per m^2 body surface area; however, younger children (e.g., age ≤8 years) may require a higher dosage (i.e., 200 mg per m^2 of body surface area twice daily, maximum dose 200 mg twice daily).

Adolescent/Adult dose: 200 mg twice daily.

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

Dosing of NVP in patients with renal failure receiving hemodialysis: For patients with renal failure on chronic 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.

NVP in combination with lopinavir (LPV)/ritonavir (RTV) (adults >18 years): 600 mg LPV/150 mg RTV (3 adult tablets) twice daily + 200 mg NVP twice daily may be considered in treatment-experienced patients where decreased sensitivity to lopinavir is suspected due to clinical history or documented by resistance testing.

NVP in combination with LPV/RTV (children ages 6 months to 18 years): see dosing tables under **Lopinavir/Ritonavir**; (LPV/RTV dosing differs when used in combination with NVP) + 150 mg per m^2 of body surface area NVP twice daily (maximum 200 mg twice daily).

NVP in combination with maraviroc (MVC) (adults): MVC 300 mg twice daily + 200 mg NVP twice daily.

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

More common: Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. NVP should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases.

Less common (more severe): Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy; may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for NVP-related hepatic toxicity in adults include: baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Drug Interactions

See: **Tables 14, 15b, and 16b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, with a 1.5–2-

fold increase in clearance. There is potential for multiple drug interactions.

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Atazanavir: NVP should not be coadministered to patients receiving ATV (with or without RTV).

Special Instructions

- Can be given without regard to food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. However, the risk of developing resistance with extended lead-in dosing is unknown and is a concern that must be weighed against the patient's overall tolerability of the regimen and the current antiviral response. NVP should be discontinued immediately and not restarted in patients who develop severe rash, a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash accompanied by elevated hepatic transaminases.
- If NVP dosing is interrupted for >7 days, NVP dosing should be restarted with once daily dosing for 14 days, followed by escalation to the full, twice daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure; patients with symptoms or signs of hepatitis should have liver function tests performed. Patients should be instructed to contact their HIV specialist if signs or symptoms develop to determine the need for evaluation. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.
- For suspension: Must be shaken well; store at room temperature.

Protease Inhibitors (PIs) * †¶

Atazanavir *(ATV, REYATAZ)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

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

Dosing

Neonatal/Infant dose: Not approved for use in neonates/infants. Should not be administered to infants <3 months of age due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose: Approved for use in children aged 6–18 years:

Weight 15 to <25 kg: ATV 150 mg + ritonavir (RTV) 80 mg, both given once daily with food

Weight 25 to <32 kg: ATV 200 mg + RTV 100 mg, both given once daily with food

Weight 32 to <39 kg: ATV 250 mg + RTV 100 mg, both given once daily with food

Weight ≥39 kg: ATV 300 mg + RTV 100 mg, both given once daily with food

For treatment-naive pediatric patients of age ≥13 years and weight >39 kg who do not tolerate RTV: may use ATV 400 mg given once daily (without RTV) with food.*

*Note: Dosing ATV with RTV is preferred; however, data from the ongoing IMPAACT/PACTG 1020A phase II study of ATV +/- RTV indicate that, if unboosted ATV is used, higher doses (on a per kg or m^2 basis) are required to achieve the target drug levels in the study. See **Supplement I: Pediatric Antiretroviral Drug Information** section on ATV for the specific dosing employed in 1020A.

Adolescent (age ≥16-21 years) /Adult dose:

Antiretroviral-naïve patients: ATV 400 mg (two 200 mg capsules) once daily with food or ATV 300 mg (one 300 mg capsule or two 150 mg capsules) + RTV 100 mg once daily with food.

Antiretroviral-experienced patients: ATV 300 mg (one 300 mg capsule or two 150 mg capsules) + RTV 100 mg once daily with food.

ATV in combination with efavirenz (EFV) (adults) in therapy-naïve patients only: 400 mg ATV + 100 mg RTV + 600 mg EFV, all once daily but at separate times. While ATV/RTV 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): 300 mg ATV + 100 mg RTV + 300 mg TDF, all once daily with food. Only RTV-boosted ATV should be used in combination with TDF.

ATV in combination with maraviroc (MVC) (adults): 300 mg ATV + 100 mg RTV once daily with food + 150 mg MVC twice daily.

Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for adjustment of dosage in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.

Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment unless they have end stage renal disease managed with hemodialysis. Treatment-naïve adult patients with end stage renal disease on hemodialysis should receive 300 mg ATV + 100mg RTV. ATV should not be given to treatment-experienced patients with end stage renal disease on hemodialysis.

Major Toxicities

More common: Asymptomatic elevations in indirect bilirubin, jaundice, headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.

Less common (more severe): 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 include life-threatening Stevens-Johnson syndrome. Fat redistribution and lipid abnormalities may be less common than with other PIs.

Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or C are at increased risk).

Drug Interactions

See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

Metabolism: ATV is both a substrate and an inhibitor of the CYP3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. ATV also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions. ATV inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). ATV is a weak inhibitor of CYP2C8.

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *NRTIs:* TDF decreases ATV plasma concentrations. Only RTV-boosted ATV should be used in combination with TDF.
- *NNRTIs:* EFV and NVP decrease ATV plasma concentrations significantly. NVP should not be coadministered to patients receiving ATV (with or without RTV). EFV should not be coadministered with ATV in treatment-experienced patients but may be used in treatment-naïve patients with RTV boosting.

Absorption*:*

- *Antacids:* Antacids and buffered medications (including buffered didanosine [ddI] formulations) decrease ATV concentrations if administered at the same time; ATV should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted ATV in treatment-naïve patients):* H2-receptor antagonists are expected to decrease ATV concentrations by interfering with absorption. ATV 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2-receptor antagonist (no single dose should exceed a dose comparable to famotidine 20 mg and total daily dose should not exceed a dose comparable to famotidine 40 mg).

- *H2-Receptor Antagonists (boosted ATV in treatment-naïve or experienced patients)*: H2-receptor antagonists are expected to decrease ATV concentrations by interfering with absorption. Dose recommendations for H2-receptor antagonists are either a ≤40 mg dose equivalent of famotidine twice daily (treatment-naïve patients) or a ≤20 mg dose equivalent famotidine twice daily (treatment-experienced patients). 300 mg ATV + 100 mg RTV should be administered simultaneously with and/or ≥10 hours after the dose of the H2-receptor antagonist.
- *H2-Receptor Antagonists (boosted ATV with tenofovir)*: In treatment-experienced patients, if tenofovir is used with H2 receptor antagonists, an increased dose of ATV should be given: 400 mg ATV + 100 mg RTV + 300 mg TDF.
- *Proton-pump Inhibitors:* Coadministration of ATV with proton-pump inhibitors is expected to substantially decrease ATV plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naïve patients are ≤20 mg dose equivalent of omeprazole taken approximately 12 hours prior to 300 mg ATV + 100 mg RTV. Coadministration of ATV and proton-pump inhibitors is not recommended in treatment-experienced patients though one study noted adequate ATV levels when a dose of 400 mg ATV + 100 mg RTV was given at the same time, or 12 hours after, a dose of 20 mg of omeprazole.

Special Instructions

- ATV should be administered with food to enhance absorption.
- Unboosted ATV does not appear to increase cholesterol or triglyceride levels. However, boosted ATV may be associated with lipid abnormalities.
- Because ATV can prolong the electrocardiogram PR interval, it should be used 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); however, in P1020A, there was no evidence that ATV combined with low dose RTV increased the risk of PR interval prolongation.
- Patients taking antacids or the buffered formulation of ddI should take ATV at least 2 hours before or 1 hour after antacid or ddI administration.
- Individuals with HBV or HCV infections and individuals with marked elevations in transaminases prior to treatment may be at increased risk for further elevations in transaminases or hepatic decompensation.

Darunavir (*DRV, TMC 114, PREZISTA*)

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 75 mg, 400 mg, and 600 mg.

Dosing

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

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

Pediatric (ages 3 to <6 year of age): Safety and efficacy has not been established.

Pediatric (ages 6 to <18 years and weighing at least 20 kg):

WEIGHT (kg)	DOSE (both twice daily with food)
≥20 to <30 kg	DRV 375 mg (five 75 mg tablets) + RTV 50 mg (0.6 ml of 80 mg/ml)
≥30 to <40 kg	DRV 450 mg (six 75 mg tablets) + RTV 60 mg (0.8 ml of 80 mg/ml)
≥40 kg	DRV 600 mg (one 600 mg tablet) + RTV 100 mg (one 100 mg gelcap)

Do not use once daily dosing in pediatric patients

Adolescent (age ≥18 years)/Adult dose (treatment-naïve): DRV 800 mg (two 400 mg tablets) + RTV 100 mg once daily, with food.

Adolescent (age ≥18 years)/Adult dose (treatment-experienced): DRV 600 mg (one 600 mg tablet) + RTV 100 mg both twice daily with food. DRV should not be used without RTV.

Dosing of DRV in combination with maraviroc (MVC) (adults): DRV 600 mg (one 600 mg tablet) + RTV 100 mg both twice daily with food + 150 mg MVC twice daily.

Dosing in patients with hepatic impairment: DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when

administering RTV-boosted DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.

Dosing in patients with renal impairment: No dose adjustment is required in patients with moderate renal impairment (CrCl 30–60 mL/min). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

Major Toxicities
More common: Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.

Less common: Skin rash, including erythema multiforme and Stevens-Johnson syndrome, 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, 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).

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism:* DRV is primarily metabolized by cytochrome P450 3A4. RTV inhibits CYP3A4, thereby increasing the plasma concentration of DRV. There is the potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer DRV with food, which increases AUC and C_{max} by 30%. The number of calories and fat content of the meal does not significantly alter drug exposure.
- DRV contains a sulfa moiety. The potential for cross-sensitivity between DRV and other drugs in the sulfonamide class is unknown. DRV should be used with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75 mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store at room temperature (25ºC or 77ºF)

Fosamprenavir *(f-APV, LEXIVA)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 700 mg f-APV calcium (prodrug, equivalent to 600 mg APV). Oral suspension, 50 mg/mL (prodrug, equivalent to 43 mg APV/mL).

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

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

Antiretroviral-naïve patient (age 2–5 years): 30 mg/kg (max dose 1400 mg) twice daily.

Antiretroviral-naïve patient (age >6 years): 30 mg/kg (max.dose 1400 mg) twice daily (without ritonavir [RTV]) *OR* 18 mg/kg (max.dose 700 mg) + RTV 3 mg/kg (max. dose 100 mg) twice daily.

Antiretroviral-experienced patients (age >6 years): 18 mg/kg (max.dose 700 mg) + RTV 3 mg/kg (max. dose 100 mg) twice daily.

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

Adult dose: Dosing regimen depends on whether the patient is antiretroviral naïve or experienced:

Antiretroviral-naïve patients:
1,400 mg f-APV twice daily (without RTV) *OR*
1,400 mg f-APV + 200 mg RTV, both given once daily *OR*

1,400 mg f-APV + 100 mg RTV, both given once daily *OR*
700 mg f-APV + 100 mg RTV, both given twice daily

Protease inhibitor-experienced patient: (Note: Once daily administration of f-APV + RTV is not recommended in PI-experienced patients.)
700 mg f-APV + 100 mg RTV, both given twice daily

f-APV in combination with efavirenz (EFV) (adults): 700 mg f-APV + 100 mg RTV twice daily + 600 mg EFV once daily; or 1,400 mg f-APV + 300 mg RTV + 600 mg EFV, all once daily (PI-naïve patients only). Only boosted f-APV with RTV should be used in combination with EFV.

f-APV in combination with maraviroc (MVC) (adults): 700 mg f-APV + 100 mg RTV twice daily + 150 mg MVC twice daily.

Dosing of f-APV in patients with hepatic impairment: Decreased dosage should be used in patients with mild to moderate hepatic impairment receiving f-APV without RTV (recommended dose for adults is 700 mg twice daily). f-APV should not be used in adult or pediatric patients with severe hepatic impairment. There are no data on the use of f-APV in combination with RTV in adult or pediatric patients with any degree of hepatic impairment and it is not recommended at this time.

Major Toxicities
More common: Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities.

Less common (more severe): Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat redistribution, 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, and elevation in serum transaminases.

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

(Note: drug interactions listed below are primarily from studies done with APV because f-APV is rapidly metabolized to APV.)

- *Metabolism:* APV is a substrate for and an inhibitor of the cytochrome P450 isoenzyme CYP3A4. Data also suggest that APV is an inducer of CYP3A4. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions
- Tablets may be taken with or without food. Adults should take the suspension without food. Pediatric patients should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take APV at least 1 hour before or after antacid or ddI use.
- APV is a sulfonamide. The potential for cross-sensitivity between APV and other drugs in the sulfonamide class is unknown. APV should be used with caution in patients with sulfonamide allergy.
- For oral suspension, shake well prior to use. Refrigeration is not required.

Indinavir *(IDV, CRIXIVAN)*
See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 100 mg, 200 mg, 333 mg, and 400 mg (corresponding to 125 mg, 250 mg, 416.3 mg, and 500 mg IDV sulfate, respectively).

Dosing
Neonatal/Infant dose: Not approved for use in neonates/infants. Should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus).
Pediatric dose: Not approved for use in children. Some clinical studies have been conducted in children (investigational dose: 500 mg per m^2 of body surface area every 8 hours in children aged 4–15 years. This dose resulted in IDV AUC levels slightly higher than achieved with standard doses in adults, but trough levels below those observed in adults, in 50% of 28 children).

Adolescent/Adult dose: 800 mg every 8 hours.

IDV in combination with ritonavir (RTV) (adults): 800 mg IDV + 100 or 200 mg RTV every 12 hours.

IDV in combination with efavirenz (EFV) (adults): 1000 mg IDV three times daily + 600 mg EFV once daily (higher doses of IDV are required).

Dosing of IDV 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.

Major Toxicities
More common: Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritis, and rash. Nephrolithiasis/urolithiasis with IDV crystal deposits: cumulative frequency is higher in children (29%) than adults (12.4%).

Less common (more severe): Fat redistribution.

Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer on an empty stomach 1 hour before or 2 hours after a meal (or can be administered 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 offluid daily in adult patients).
- If coadministered with didanosine, give ≥1 hour apart on an empty stomach.
- Capsules are sensitive to moisture and should be stored at room temperature (59–86ºF) in original container with desiccant.

Lopinavir/Ritonavir *(LPV/RTV, ABT 378, KALETRA)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Coformulation of LPV/RTV: RTV acts as a pharmacokinetic enhancer, not as an antiretroviral agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

Preparations: Tablets: 200 mg LPV/50 mg RTV and pediatric tablets 100 mg LPV/25 mg RTV. Pediatric oral solution (note: contains 42.4% alcohol by volume): 80 mg LPV/20 mg RTV per mL.

Dosing
Neonatal/Infant dose (infants aged 14 days to 6 months): Approved for use in infants 14 days of age or older; once daily administration is not recommended. The recommended dose of the oral solution is 300 mg LPV per m^2 of body surface area/75 mg RTV per m^2 body surface area, or 16 mg LPV per kg body weight/4 mg RTV per kg body weight twice daily. Because there are no data for dosage of LPV/RTV administered with efavirenz (EFV), nevirapine (NVP), fosamprenavir (f-APV), or nelfinavir (NFV) in infants age <6 months, it is recommended LPV/RTV not be administered in combination with these drugs in such infants.

> NOTE: Use of 300 mg LPV per m^2 of body surface area in infants age <6 months, particularly those age <6 weeks, is associated with lower trough levels in children than in adults; infants should be evaluated and LPV dosing adjusted for incremental growth at frequent intervals (see **Supplement I: Pediatric Antiretroviral Drug Information** for discussion).

Pediatric Dosing

For individuals not receiving concomitant NVP, EFV, f-APV, or NFV:

Pediatric dose (age ≥6 months to 18 years): Once daily dosing is not recommended.

Dosing for 100 mg LPV/25 mg RTV Pediatric Tablets for Children Age 6 Months to 18 Years Given WITH Concomitant Efavirenz, Nevirapine, Fosamprenavir, or Nelfinavir		
Body Weight (kg)	Body Surface Area (meter^2)*	Recommended Number of 100 mg LPV/25 mg RTV Tablets Given Twice-Daily
15 to 20 kg	≥0.6 to <0.8	2
>20 to 30 kg	≥0.8 to <1.2	3
>30 to 45 kg	≥1.2 to <1.7	4 (or two 200 mg LPV/50 mg RTV tablets)
>45 kg	≥1.7	4 or 6 (or two or three 200 mg LPV/50 mg RTV adult tablets)**

Body surface area dosing: 230 mg LPV per m^2 of body of surface area /57.5 mg RTV per m^2 of body surface area per dose twice daily.

Weight based dosing: <15 kg: 12 mg LPV per kg body weight/3 mg RTV per kg body weight per dose twice daily; ≥15 kg to 40 kg: 10 mg LPV per kg body weight/2.5 mg RTV per kg body weight per dose twice daily.

*Oral solution is available for children with a body surface area <0.6 m^2 or those who are unable to reliability swallow a tablet; dosing should be calculated based on body surface area or weight as per above.

NOTE: Use of 230 mg LPV per m^2 of body surface area in children is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but is associated with lower trough levels in children than in adults; therefore some clinicians may opt to initiate therapy with higher doses of LPV/RTV (see **Supplement I: Pediatric Antiretroviral Drug Information** for discussion of dosing).

Adult (age >18 years) dose, antiretroviral-naïve patients: 800 mg LPV/200 mg RTV once daily with food. Use once daily regimen only in antiretroviral-naïve patients. Do not use once daily dosing in children or adolescents. Once daily dosing should not be used in patients receiving concomitant therapy with EFV, NVP, f-APV, or NFV.

For individuals receiving concomitant NVP, EFV, f-APV, or NFV (these drugs induce LPV metabolism, reduce LPV plasma levels, and require increased LPV/RTV dosing) and/or treatment-experienced patients in whom reduced susceptibility to LPV is suspected (such as those with prior treatment with other PIs):

Pediatric dose (age ≥6 months to 18 years) with NVP, EFV, f-APV, or NFV: Once daily dosing is not recommended.

Dosing for 100 mg LPV/25 mg RTV Pediatric Tablets for Children/Adolescents Age 6 Months to 18 Years Given WITHOUT Concomitant EFV, NVP, f-APV, or NFV		
Body Weight (kg)	Body Surface Area (m^2)*	Recommended Number of 100 mg LPV/25 mg RTV Tablets Given Twice-Daily
15 to 25 kg	≥0.6 to <0.9	2
>25 to 35 kg	≥0.9 to <1.4	3
>35 kg	≥1.4	4 (or two 200 mg LPV/50 mg RTV adult tablets)

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

Weight based dosing: <15 kg: 13 mg LPV per kg body weight/3.25 RTV per kg body weight per dose twice daily; ≥15 kg to 45 kg: 11 mg LPV per kg body weight/2.7 mg RTV per kg body weight per dose twice daily.

*Oral solution is available for children with a body surface area <0.6 m^2 or those who are unable to reliably swallow a tablet; dosing should be calculated based on body surface area or weight as per above.
**The higher dose may be considered in treatment-experienced patients where decreased sensitivity to LPV is suspected due to clinical history or documented by resistance testing.

NOTE: Use of 300 mg per m2 of body surface area in children (when coadministered with NVP, EFV, f-APV, or NFV) is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults; therefore, some clinicians may choose to initiate therapy with high doses of LPV/RTV when coadministered with these drugs, particularly in PI-experienced pediatric patients who may have reduced PI

susceptibility (see **Supplement I: Pediatric Antiretroviral Drug Information** for discussion).

Adult dose (age >18 years) (if receiving concomitant NVP, EFV, f-APV, or NFV): 600 mg LPV/150 mg RTV twice daily. Once daily dosing should not be used.

LPV/RTV in combination with saquinavir (SQV) hard gel capsules (INVIRASE) (adults): 1,000 mg SQV + 400 mg LPV/100 mg RTV, both given twice daily.

LPV/RTV dosing in combination with maraviroc (MVC) (adults): 400 mg LPV/100 mg RTV twice daily + 150 mg MVC twice daily.

Dosing of LPV/RTV in patients with hepatic impairment: LPV/RTV is primarily metabolized by the liver. Caution should be used when administering this drug to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.

Major Toxicities
More common: Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving LPV/RTV with other antiretroviral drugs; lipid abnormalities.

Less common (more severe): Fat redistribution.

Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases).

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: LPV/RTV is extensively metabolized by hepatic cytochrome P450. There is potential for multiple drug interactions.[§]
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- LPV/RTV tablets can be administered without regard to food.
- LPV/RTV tablets must be swallowed whole. Do not crush or split tablets.
- LPV/RTV oral solution should be administered with food. A high fat meal increases absorption, especially of the liquid preparation.
- If coadministered with didanosine (ddI), ddI should be given 1 hour before or 2 hours after LPV/RTV.
- LPV/RTV oral solution should be refrigerated. Can be kept at room temperature up to 77ºF (25ºC) if used within 2 months.

Nelfinavir *(NFV, VIRACEPT)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 250 mg and 625 mg. Powder for oral suspension: 50 mg per one level gram scoop full (200 mg per one level teaspoon) (oral powder contains 11.2 mg phenylalanine per gram of powder).

Dosing
Neonatal/Infant dose: Not approved for use in neonates/infants. High inter-patient variability in drug concentrations was seen with 40 mg NFV per kg of body weight twice daily in infants aged birth to age 6 weeks. NFV is best absorbed when administered with a high fat meal, creating difficulty in dosing of young infants. Higher doses are currently under investigation.

Pediatric dose (age 2–13 years): 45–55 mg per kg of body weight twice daily or 25–35 mg/kg 3 times daily.*

Adolescent/Adult dose: 1,250 mg (five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) 3 times daily.
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 elevation in serum transaminases.

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: NFV is metabolized in part by cytochrome P450 3A4 (CYP3A4). There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer with meal or light snack.
- If coadministered with ddI, NFV should be administered 2 hours before or 1 hour after ddI.
- For powder for oral suspension: powder may be mixed with water, milk, pudding, ice cream, or formula; mixture is stable for up to 6 hours.
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Patients unable to swallow the tablets can dissolve the tablets in a small amount of water. Once dissolved, the 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.

Ritonavir *(RTV, NORVIR)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 100 mg. Oral solution (note: contains 43% alcohol by volume): 80 mg/mL.

Dosing
Ritonavir as a pharmacokinetic enhancer: The major use of RTV is as a pharmacokinetic enhancer of other PIs. The dose of ritonavir recommended varies with the different protease inhibitors. See dosing information for specific PI.

Neonatal/Infant dose: Not approved for use in neonates/infants aged ≤1 month. (Investigational dose: 450 mg RTV per m^2 of body of surface area twice daily was associated with lower RTV concentrations than observed in adults receiving the standard adult dose).

Pediatric (age >1 month) usual dose: The full dose of 350–450 mg per m^2 of body surface area twice daily (maximum dose of 600 mg) is recommended in the unusual situation when RTV is prescribed as the sole PI. Dose escalation over several days is recommended to minimize gastrointestinal toxicity.

Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase stepwise to full dose over 5 days as tolerated.

Dosing of RTV in patients with hepatic impairment: RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data for dosing adult or pediatric patients with severe hepatic impairment; caution should be used when administering this drug to patients with moderate-to-severe hepatic impairment.

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 redistribution.

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. Prolongation of the PR interval and second or third degree atrioventricular block.

Drug Interactions
See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: RTV is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions.

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions and overlapping toxicities.

Special Instructions

- Administration with food increases absorption and helps decrease gastrointestinal side effects.
- If RTV is prescribed with didanosine (ddI), there should be 2 hours between taking each of the drugs.
- It is recommended that the soft gelatin capsules be stored in the refrigerator at 36–46°F (2–8°C) until dispensed. Refrigeration of the capsules by the patient is recommended, but not required if capsules are used within 30 days and stored below 77°F (25°C).
- Recommended storage of the oral solution is at room temperature 68–77°F (20–25°C). Do not refrigerate. Shake well before use.
- Oral solution has limited shelf-life (6 months); use by product expiration date.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose as tolerated.

Techniques to increase tolerance in children:

- Mix oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream;
- Dull the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates;
- Coat the mouth by giving peanut butter to eat before the dose; or
- Administer strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.

Saquinavir *(SQV, INVIRASE hard gel capsule or film-coated tablets)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Hard gel capsules (HGC): 200 mg; Film-coated tablets: 500 mg.

Dosing

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

Pediatric dose: Not approved for use in children. Clinical trials in children demonstrated that doses of 50 mg SQV per kg of body weight every 8 hours were inadequate to achieve therapeutic serum SQV concentrations. Clinical trials are under way in children to evaluate administration of SQV in combination with a second PI, such as ritonavir (RTV), nelfinavir, or lopinavir (LPV)/RTV. SQV should not be used as a sole PI in children.

Adolescent (age >16 years)/Adult dose: SQV in combination with RTV (adults): 1000 mg SQV + 100 mg RTV, both given twice daily. Should be taken within 2 hours after a full meal. Note: SQV should only be used in combination with RTV or LPV/RTV (never unboosted).

SQV in combination with LPV/RTV (adults): 1,000 mg SQV + 400 mg LPV/100 mg RTV, both given twice daily.

SQV in combination with maraviroc (MVC) (adults): 1000 mg SQV + 100 mg RTV, both given twice daily + MVC 150 mg twice daily.

Dosing of SQV in patients with hepatic impairment: Use with caution in patients with hepatic impairment.

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 redistribution.

Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases.

Drug Interactions

See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: SQV is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there is potential for numerous drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer within 2 hours after a full meal to increase absorption.
- Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended.
- SQV should only be used in combination with RTV or LPV/RTV (never unboosted).

Tipranavir (*TPV, APTIVUS)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 250 mg. Pediatric oral solution (Note: contains 116 International Units [IU] vitamin E per mL): 100 mg TPV per mL.

Dosing

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

Pediatric dose: *(age 2-18 years)*: Must be coadministered with ritonavir (RTV).

Body surface area dosing: 375 mg TPV per m^2 body surface area per dose coadministered with 150 mg RTV per m^2 body surface area per dose, both twice daily (maximum dose TPV 500 mg + RTV 200 mg twice daily).

Weight-based dosing: 14 mg TPV per kg body weight per dose coadministered with 6 mg RTV per kg body weight per dose, both twice daily (maximum dose TPV 500 mg + RTV 200 mg twice daily).

NOTE: For patients with intolerance or toxicity and who do not have virus resistant to more than one PI, a dose reduction can be considered:

Body surface area dosing: 290 mg TPV per m^2 body surface area per dose coadministered with 115 mg RTV per m^2 body surface area per dose, both twice daily.

Weight-based dosing: 12 mg TPV per kg body weight per dose coadministered with 5 mg RTV per kg body weight per dose, both twice daily.

Dose reduction is not appropriate if virus is resistant to more than one PI.

Adult dose: 500 mg (two 250 mg capsules) coadministered with 200 mg of RTV, twice daily.

Dosing of TPV in patients with hepatic impairment: No dosing adjustment is required in patients with mild hepatic impairment. TPV is contraindicated in patients with moderate or severe hepatic insufficiency.

Dosing of TPV with maraviroc (MVC) (adults): 500 mg (two 250 mg capsules) coadministered with 200 mg of RTV, twice daily + MVC 300 mg twice daily.

Major Toxicities

More common: Diarrhea, nausea, fatigue, headache, rash (more frequent in children than adults), and vomiting. Laboratory abnormalities are elevated liver enzymes, cholesterol, and triglycerides.

Less common (more severe): Fat redistribution. Clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or C coinfection or elevations in transaminases are at increased risk for developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.

Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Possible association with increased risk of intracranial hemorrhage.

Drug Interactions

See: **Tables 14, 15a, and 16a** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Metabolism*: TPV is metabolized in part by cytochrome P450 3A4. There is potential for multiple drug interactions.[§]
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Tipranavir can be taken with or without food. However, it is recommended that RTV be taken with food and the combination may be better tolerated if taken with a meal or snack.
- The oral solution contains 116 IU per mL of vitamin E, which is significantly higher than the

reference daily intake for vitamin E for children or adults (pediatrics 10 IU, adults 30 IU). The recommended dose of TPV (14 mg per kg body weight) results in a vitamin E dose of 16 IU per kg body weight per day. Patients taking the oral solution should not take any supplemental vitamin E greater than a standard multivitamin.

- TPV is indicated only in patients who are highly treatment experienced or have HIV-1 strains resistant to multiple PIs, and who have evidence of viral replication.
- TPV contains a sulfonamide component. The potential for cross-sensitivity between TPV and other drugs in the sulfonamide class is unknown. TPV should be used with caution in patients with sulfonamide allergy.
- Oral solution should be stored at room temperature (e.g., 77° F); do not refrigerate or freeze. Must use oral solution within 60 days after first opening bottle.
- Capsules should be refrigerated. Can be kept at room temperature up to 77ºF (25ºC) if used within 2 months.
- Because TPV can cause serious liver toxicity, liver function tests should be performed at initiation of therapy and monitored frequently.
- TPV 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 and anticoagulants, or who are taking supplemental high doses of vitamin E.

Entry Inhibitors

Maraviroc *(MVC, SELZENTRY)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 150 mg and 300 mg.

Dosing

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

Pediatric dose: Not approved for use in children aged <16 years. No data currently available on dosage below this age.

Adolescent (≥16 years)/Adult dose:

When given with strong CYP3A4 inhibitors (with or without CYP3A inducers) including all PIs (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, and clarithromycin	150 mg twice daily
When given with other drugs that are not strong inhibitors or inducers of CYP3A4 such as all the NRTIs, enfuvirtide, tipranavir/ritonavir, and nevirapine	300 mg twice daily
When given with CYP3A inducers including efavirenz , rifampin, carbamazepine, phenobarbital, and phenytoin (without a strong CYP3A inhibitor)	600 mg twice daily

Major Toxicities

More common: Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.

Less common (more severe): Serious adverse events occurred in less than 2% of MVC-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.

Dosing of MVC in patients with hepatic impairment: MVC has not been sufficiently studied in patients with hepatic impairment, and it has not been studied in patients with severe hepatic impairment. Because MVC is metabolized by the liver, concentrations may be increased.

Dosing of MVC in patients with renal impairment: Dosing of MVC in patients with renal impairment has not been studied. Patients with CrCl <50 mL/min receiving CYP3A inhibitors may be increased risk of MVC toxicity.

Drug Interactions

See: **Tables 14, 15d, and 16b** from the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***

- *Absorption:* Absorption of maraviroc is somewhat reduced in the presence of a high fat meal, but no food restrictions were imposed during clinical trials.
- *Metabolism:* Maraviroc is a cytochrome P450 (CYP) 3A and p-glycoprotein (Pgp) substrate and

may require dosage adjustments when administered with CYP- or Pgp-modulating medications.

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- An HIV tropism assay is required prior to use to exclude the presence of CXCR4-using or mixed/dual tropic HIV.
- Can be given without regard to food.
- Patients need to be instructed on how to recognize symptoms of allergic reactions or hepatitis.
- Caution should be used when administering MVC to patients with underlying hepatic dysfunction or those patients co-infected with hepatitis B or C.
- Caution should be used when administering MVC to patients with underlying cardiac disease.
- Caution should be used when administering MVC to patients receiving CYP3A inhibitors who have CrCl<50 mL/min.
- Caution should be used when administering MVC to patients receiving CYP3A inhibitors who have moderate hepatic impairment. These patients require close monitoring for maraviroc associated adverse effects.

Fusion Inhibitors

Enfuvirtide *(FUZEON, T-20)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Injection: lyophilized powder for injection, 108 mg of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience Kit: 60 single use vials of Fuzeon (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes.

Dosing

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

Pediatric/adolescent dose (age 6–16 years): Not approved for use in children aged <6 years. For children aged ≥6 years: 2 mg per kg of body weight (maximum dose, 90 mg [1 mL]) given twice daily, injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Adolescent (age >16 years)/Adult dose: 90 mg (1mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Major Toxicities

Most common: Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.

Less common: Increased rate of bacterial pneumonia (unclear association) and local site cellulitis (3%–8%).

Rare: Hypersensitivity reactions (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with hypersensitivity reactions.

Drug Interactions

- There are no known significant drug interactions.

Special Instructions

- Patients or caregivers should be carefully instructed in proper technique for drug reconstitution and administration of subcutaneous injections. Fuzeon injection instructions are provided with convenience kits.
- Reconstituted vial should be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, Fuzeon should be injected immediately or kept refrigerated in the original vial until use. Reconstituted Fuzeon must be used within 24 hours.

- Must be given subcutaneously; severity of reactions increased if given intramuscularly.
- Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel.
- Careful monitoring for signs and symptoms of local infection or cellulitis should be done by both the patient/caregiver and health care provider.
- Tips to minimize local reactions: Apply ice or heat after injection or gently massage injection site to better disperse the dose. There are some reports of injection site reactions if alternative delivery systems (e.g., Biojector) are used.
- Patients/caregivers should be advised of the possibility of a hypersensitivity reaction and should discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a hypersensitivity reaction.

Integrase Inhibitors

Raltegravir *(MK-0518, RGV, RAL, ISENTRESS)*

See also: **Supplement I: Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 400mg.

Dosing

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

Pediatric dose: Not approved for use in children aged <16 years. Currently in phase I/II study in IMPAACT P1066 for children aged 2–18 years.

Adolescent (age ≥16)/Adult dose: RAL 400 mg twice daily.

Dosing of RAL in patients with hepatic insufficiency: 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.

Major Toxicities

More common: Nausea, headache, dizziness, diarrhea, fatigue, and itching.

Less common: Abdominal pain, vomiting. In patients coinfected with chronic active hepatitis B and/or C, worsening of laboratory abnormalities from baseline AST, ALT, or total bilirubin more likely than in patients not coinfected.

Rare: Creatine kinase elevations (grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Caution is advised in patients receiving medications associated with these toxicities.

Drug Interactions

See: **Tables 15e** from 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 uridine diphosphate glucoronosyltransferase (UGT1A1). Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of RAL while inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of RAL.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Can be given without regard to food.

ENDNOTES

[*] Information in this appendix is not all-inclusive. Complete and detailed prescribing and toxicity information for these drugs is available from the drug companies and should be reviewed by the health care provider before prescribing these drugs.

[†] Adolescents in early puberty (Tanner Stage I − II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage IV) should be dosed using adult schedules. Youth who are in the midst of a growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

§ Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions with multiple drugs. Some of these may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review the prescribing information for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

¶ PI dosing data in children are limited, and doses may change as more information is obtained about the pharmacokinetics of these drugs in children.

APPENDIX C: Pediatric Antiretroviral Guidelines Working Group Conflict of Interest Disclosure – 2008

NAME	PANEL STATUS*	COMPANY	RELATIONSHIP
Elaine Abrams	M	NONE	N/A
Carolyn Burr	S	NONE	N/A
Edmund Capparelli	M	Arpida Pharmaceuticals Cadence Pharmaceuticals Elan Pharmaceuticals Glaxo Smith Kline InfraCare Mpex Pharmaceuticals Pfizer Wyeth Pharmaceuticals	• Consultant • Consultant • Consultant • Consultant • Consultant • Consultant • DSMB member (compensation <$10,000 yearly) • Consultant
Diana Clarke	M	NONE	N/A
Kenneth Dominguez	GR	Antiretroviral Pregnancy Registry (administered by Kendle International, Co)	• Advisory Board Member
Brian Feit	GR	NONE	N/A
Pat Flynn	M	Medimmune Tibotec	• Clinical Trial Agreement • Clinical Trial Agreement
Marc Foca	M	Celestis	• Honoraria
Ed Handelsman	GR	NONE	N/A
Peter Havens	C	NONE	N/A
Rohan Hazra	GR	NONE	N/A
Nancy Hutton	M	NONE	N/A
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Mark Mirochnick	M	Glaxo Smith Kline	• Clinical Trial Contract
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Geoffrey Weinberg	C	Astellas Pharma US MedImmune, Inc Merck & Co, Inc NY State Dept of Health AIDS Institute Sanofi Pasteur, Inc	• Grant recipient • Grant recipient; Advisory Board member • Speakers' Bureau • Consultant; Advisory Board member; honoraria • Speakers Bureau
Andrew Wiznia	M	Abbott Pharmaceuticals Gilead Sciences Glaxo Smith Kline Merck & Co, Inc Tibotec Pharmaceuticals	• Honoraria • Grant recipient, Consultant • Grant recipient • Grant recipient • Grant recipient, Consultant

* C=Co-Chair; M=member; GR=government representative; S=staff; N/A=not applicable.